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Clinical, cognitive, and neuroimaging correlates of risk for postpartum psychosis

Pauls, Astrid

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Clinical, cognitive, and neuroimaging correlates of risk for postpartum psychosis

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Thesis submitted in partial fulfilment of the requirements of King's
College London University for the degree of Doctor in Philosophy

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This thesis is dedicated to my daughter Lily Mae

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Abstract

Although postpartum psychosis is a devastating and predictable disorder, it has received little attention in biological research. This is the first study assessing cognitive, emotional and neuroimaging correlates of women at risk of postpartum psychosis. We hypothesised that women “at risk” will show decreased brain activation in the dorsolateral prefrontal cortex in a working memory task and increased brain activation in the amygdala in a facial emotion processing task, compared to healthy controls, similar to that observed in bipolar disorder and psychoses unrelated to childbirth.

Twenty-five women “at risk” (N=13 due to non-postpartum and N=12 due to postpartum episodes) were compared to 21 healthy women within the first year after delivery. Women took part in two study visits including clinical interviews and a magnetic resonance imaging (MRI) scan. We assessed working memory and emotional face processing using two functional MRI tasks and verbal memory using two behavioural tasks.

Groups were matched on sociodemographic background and medical and obstetric history. Women “at risk” showed an activation increase of the midcingulate and temporal cortices compared to healthy controls, which was accompanied by deficits in working and verbal memory performance. Women with postpartum episodes, compared to healthy controls, showed a relative increase in activation to fearful faces in the left inferior frontal gyrus.

This study provides preliminary evidence that women “at risk” of postpartum psychosis show cognitive impairments similar to those of patients with bipolar disorder and psychoses unrelated to childbirth. Women with postpartum episodes seem to differ in emotional processing from healthy controls, possibly indicating an increased emotional response to fear. These results represent a first step towards a better understanding of cognitive and emotional processes in postpartum psychosis. When validated in larger and longitudinal studies, they may help clinicians in developing individual management strategies and implementing targeted cognitive trainings or interventions.

List of abbreviations

ACTH	=	Adrenocorticotrophic hormone
AIS	=	Athens insomnia scale
ANOVA	=	Analysis of variance
AVP	=	Vasopressin
BA	=	Brodmann area
BDI	=	Beck depression inventory
BLE	=	Brief life events
BNC	=	British national corpus
BOLD	=	Blood-oxygen-level dependence
CECA-Q	=	Childhood experience of care and abuse questionnaire
CGA	=	Combined group analysis
CGI	=	Clinical global impressions
CRH	=	Corticotropin releasing hormone
CSF	=	Cerebrospinal fluid
CT	=	Computed tomography
CV	=	Clinician version
DSM	=	Diagnostic and statistical manual of mental disorders
ECT	=	Electroconvulsive therapy
EPI	=	Echo-planar imaging
FIGS	=	Family interview for genetic studies
FMRI	=	Functional magnetic resonance imaging
FWE	=	Family wise error
GAF	=	Global assessment of functioning
GH	=	Growth hormone
HAM-D	=	Hamilton depression rating scale
HC	=	Healthy control
HDR	=	Hemodynamic response
HPA	=	Hypothalamic-pituitary-adrenal
ICD	=	International classification of diseases
ILE	=	Intrusive life events
IQ	=	Intelligence quotient
LM	=	Logical memory

M	=	Mean
MarsBaR	=	MARseille Boîte À Région d'Intérêt
MHRN	=	Mental Health Research Network
MNI	=	Montreal neurological institute
MRI	=	Magnetic resonance imaging
N	=	Number
NHS	=	National health service
NPE	=	Non-postpartum episodes
NR	=	Not reported
OFC	=	Orbitofrontal cortex
PANSS	=	Positive and negative syndrome scale
PE	=	Postpartum episodes
PSS	=	Perceived stress scale
RDC	=	Research diagnostic criteria
ROI	=	Region of interest
RT	=	Reaction time
SD	=	Standard deviation
SGA	=	Sub group analysis
SPM	=	Statistical parametric mapping
SPSS	=	Statistical product and service solutions
STAI	=	State-trait anxiety inventory
VB	=	Visual basic
WMS	=	Wechsler memory scale
WTAR	=	Wechsler test of adult reading
YMRS	=	Young mania rating scale

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1. Chapter: Introduction

Postpartum psychosis is a rare, but severe postpartum disorder often occurring within the first days to weeks following childbirth (Heron, Robertson Blackmore, McGuinness, Craddock, & Jones, 2007; Sit, Rothschild, & Wisner, 2006). Symptoms typically include hallucinations, delusions, cognitive disorganisation and mood disturbances (Sit et al., 2006). Recovery is a long and difficult process and often takes up to a year (Heron et al., 2012). Frequently, women need to be hospitalised (Sharma, 2008). Postpartum psychosis is currently diagnosed under the mood disorder section or as a brief psychotic episode according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV (American Psychiatric Association, 1994). Women are often in their mid to late twenties when they experience postpartum psychosis, although it can occur at any age during the childbearing years with an incidence of 1-2/1000 women (Brockington, 1996; Sit et al., 2006). Postpartum psychosis has severe consequences for mother and child and needs to be treated as an emergency (Sit et al., 2006). Consequently, it is very important to investigate factors precipitating and accompanying postpartum psychosis.

One key issue concerning research in postpartum psychosis is the difficulty in terms of its nosology, which has led to a general paucity in research. In order to shed light onto neurobiological and neuropsychological processes implicated in postpartum psychosis, it is of great importance to investigate potential clinical, cognitive, emotional, and neuroimaging correlates of postpartum psychosis. The objective of this thesis is to assess these correlates in four experimental chapters. Before this, a theoretical background of postpartum psychosis is given, followed by a discussion of its relation to other mental disorders. This is important because having a psychiatric diagnosis is considered as a major risk factor. In addition, this section lies the theoretical background down for our selected “at risk” population. Then, biological, clinical and sociodemographic, and cognitive, emotional, and neuroimaging findings will be discussed. We propose that women with postpartum psychosis will show similar cognitive, emotional, and neuroimaging alterations as those found in bipolar disorder and other psychoses unrelated to childbirth.

1.1 Postpartum psychosis

In this chapter, the historical context and epidemiology will be reviewed.

1.1.1 Historical context

Early descriptions of postpartum psychosis (“postpartum mania or insanity, or puerperal psychosis”), found in general medical texts of the seventeenth century, describe it as severe mental illness which appears suddenly and unexpectedly after childbirth (Plater, 1602 and 1656; Schenk, 1609; in Brockington, 1996). The concept that a mental illness is triggered by childbirth seemed to have been established by the end of the eighteenth century, following which the first research data were collected (Osiander, 1797; Denman, 1801; Esquirol, 1818 and 1845; in Brockington, 1996). The first controlled studies assessing postpartum psychosis commenced in the twentieth century (Brockington, 1996; Paffenbarger, 1961, 1964; Paffenbarger & McCabe, 1966).

Postpartum psychosis is a serious disorder and given the severity of symptoms (e.g. hallucinations, confusion, or disorientation) and temporal proximity to childbirth, there is no dispute about its existence *per se*. However, the Kraepelinian classification of the “two entities principle” between schizophrenia and affective psychosis established in the nineteenth century made it difficult to *classify* postpartum psychosis in terms of its nosology (Brockington, 1996; Klompenhouwer & van Hulst, 1991; Loudon, 1988). This difficulty arises partly due to its often mixed presentation of psychotic and affective symptoms. Another reason is that having a diagnosis of bipolar or schizoaffective disorder, or to a lesser extent a history of psychosis unrelated to childbirth or schizophrenia, puts women at a higher risk of developing postpartum psychosis and vice versa (Boyce & Barriball, 2010; Harlow et al., 2007; Jones & Craddock, 2001; Nager, Szulkin, Johansson, Johansson, & Sundquist, 2012; Reich & Winokur, 1970; Sit et al., 2006). Until today, the nosological status of postpartum psychosis remains controversial (Benvenuti et al., 1992; Jones & Craddock, 2007; Klompenhouwer & van Hulst, 1991). Whether postpartum psychosis forms its own entity (i.e. a condition triggered exclusively by childbirth) or is part of another mental disorder will be further explored in section 1.2. In the following section the epidemiology will be examined.

1.1.2 Epidemiology

This section includes the current classification of postpartum psychosis according to DSM-IV, followed by a description of symptoms, incidence, onset, treatment and risks following postpartum psychosis.

1.1.2.1 Classification

In the current version of the DSM-IV, postpartum psychosis is diagnosed as either a mood disorder (major depressive, manic, mixed episode of major depressive disorder, bipolar I disorder, or bipolar II disorder) or as a brief psychotic disorder (for symptoms see section 1.1.2.3). The specified time criterion requires that the onset of symptoms should be within four weeks following delivery (American Psychiatric Association, 1994; Brockington, 1996). This time-frame is shorter than the six weeks following delivery required by the International Classification of Diseases (ICD)-10. According to the ICD-10, postpartum psychosis can be included under mental disorders associated with the puerperium if no criteria for other disorders are met (World Health Organization, 1992). These two classification systems already highlight the inconsistencies regarding postpartum psychosis between existing diagnostic manuals. Far more in agreement are the findings concerning the incidence of postpartum psychosis.

1.1.2.2 Incidence

Postpartum psychosis is quite consistently estimated to occur after 1-2/1000 deliveries (Brockington et al., 1981; Dean & Kendell, 1981; Kendell, Chalmers, & Platz, 1987; Klompenhouwer & van Hulst, 1991; R. Kumar, 1994; R. Kumar, Marks, Platz, & Yoshida, 1995; Meltzer & Kumar, 1985; Sit et al., 2006; Tschinkel, Harries, Le Noury, & Healy, 2007). The mean age of onset for postpartum psychosis has been reported to be in the mid to late twenties of an age range typically within the childbearing years of 20-40 years (P. Agrawal, Bhatia, & Malik, 1990; Dowlatshahi & Paykel, 1990; C. L. E. Katona, 1982; Reich & Winokur, 1970; Rohde & Marneros, 1993). Some variability in the rates may be explained by differences in diagnostic tools and time of onset following delivery used across research studies (ranging from a few days to up to one year).

1.1.2.3 Symptoms

Symptom presentation is inconsistent across patients, which may contribute to difficulties in establishing clear and reliable classification criteria. Symptoms can be categorised as psychotic, affective, cognitive, and other symptoms (Table 1.1). Postpartum psychosis can present itself with symptoms frequently seen in psychoses unrelated to childbirth such as delusions and hallucinations (Engqvist, Ferszt, Åhlin, & Nilsson, 2009; Rohde & Marneros, 1993; Sit et al., 2006). These symptoms can be mood congruent and incongruent (Sit et al., 2006). In the case of postpartum psychosis, it has been reported that 53-78% of the delusional ideas are related to the infant (Chandra, Bhargavaraman, Raghunandan, & Shaligram, 2006).

Table 1.1 Symptoms of postpartum psychosis

Psychotic symptoms	Affective symptoms	Cognitive symptoms	Other symptoms
Delusions	Elation	Disorganisation	No Insight
Hallucinations	Dysphoria	Confusion	Insomnia
Thought insertion	Mood lability	Perplexity	Rambling in speech
Thought broadcasting	Odd affect		Excessive activity
Experiences of alienation	Agitation		
Echo phenomena	Aggression		
Catatonic features	Depression		
Disconnection			

Other rare symptoms have been reported, such as the Capgras and the Fregoli syndromes (Cohn, Rosenblatt, & Faillace, 1977; De Leo, Galligioni, & Magni, 1985; Nilsson & Perris, 1971; O'Sullivan & Dean, 1991). The Capgras syndrome is the delusion that someone who is well known to the patient has been replaced by an imposter. Patients suffering from the Fregoli syndrome identify a familiar person in various strangers, claiming that although those have no physical resemblance, they are psychologically identical (Cohn et al., 1977; De Leo et al., 1985; Nilsson & Perris, 1971; O'Sullivan & Dean, 1991). One key symptom of postpartum psychosis, however, is cognitive disorganisation (e.g. confusion or disconnected thinking) (Kisa, Aydemir, Kurt, Gülen, & Göka, 2007; Platz & Kendell, 1988; Wisner, Peindl, & Hanusa, 1994). In addition, postpartum psychosis often presents with mixed affective symptoms (e.g. feeling like a failure at the same time as having flight of ideas) (Brockington, 1996; Brockington et al., 1981; Brockington, Margison, Schofield, & Knight, 1988; Dean & Kendell, 1981; Hanson & Brown, 1973; Jones,

2008; Jones & Craddock, 2005; Kadrmas, Winokur, & Crowe, 1979; Klompenhouwer & van Hulst, 1991; Oosthuizen, Russouw, & Roberts, 1995; Sharma, Smith, & Khan, 2004; Sit et al., 2006; Vinogradov & Csernansky, 1990). Mild hypomanic symptoms have been reported within the first day after delivery (Heron, McGuinness, Blackmore, Craddock, & Jones, 2008; Heron et al., 2007; Melges, 1968).

1.1.2.4 Onset

The time of onset of postpartum psychosis following delivery has often been reported to be within the first two to four weeks after childbirth, with a supposed “symptom free period” lasting from 24 hours to up to a week (Heron et al., 2007; Sit et al., 2006). However, an onset of symptoms within 24 hours has been reported in one of the earlier studies of postpartum psychosis (Paffenbarger, 1961). This was supported by more studies showing that in fact prodromal symptoms (reported as subjectively experienced emotional and behavioural changes) can emerge within the first three days after delivery (Heron et al., 2008; Heron et al., 2007; Melges, 1968). Subjective recall of clinically significant symptoms was investigated retrospectively in a sample of women with a previous episode of postpartum psychosis. The results of this study showed that the majority of women had a symptom onset within the first week after delivery, with 22% of the symptoms occurring within the first day and 50% within the first three days (Heron et al., 2007). These findings challenge the concept of a symptom free period after delivery in postpartum psychosis (Heron et al., 2008; Heron et al., 2007; Melges, 1968). It has been suggested that the concept of a symptom free period has emerged due to reporting the time of the women’s admission to hospital as the time of illness onset, which is logically later, rather than the actual symptom onset which may have been days before (Heron et al., 2007).

Early symptoms of postpartum psychosis include feeling excited, elated, or high (52%), not needing to sleep or not being able to sleep (48%), feeling active or energetic (37%), and talking more or feeling very chatty (31%) (Heron et al., 2008). These prodromal, often hypomanic, symptoms might have gone unnoticed by midwives, who instead may even have declared the mother as being highly functional (Heron et al., 2008). It has been proposed that a mild hypomanic state

could indeed be “adaptive”, leading to an improved general functioning of the mother and a better relationship between mother and infant. However, mild hypomanic symptoms found in healthy women following delivery were predictive of later depression as were high scores on scales quantifying depression, tears and lability (Glover, Liddle, Taylor, Adams, & Sandler, 1994; Heron, Craddock, & Jones, 2005; Heron, Haque, Oyeboode, Craddock, & Jones, 2009; Kendell, McGuire, Connor, & Cox, 1981). It seems possible that any major emotional lability following delivery, with either a manic or depressed tendency, could be an early sign for the potential development of mood problems, leading potentially to postpartum psychosis and with that to serious adverse consequences for the mother and the child (P. Agrawal et al., 1990; Dowlathshahi & Paykel, 1990; C. L. E. Katona, 1982; Reich & Winokur, 1970; Rohde & Marneros, 1993).

1.1.2.5 Adverse consequences

Following an episode of postpartum psychosis, there is a high risk of a lack of emotional bonding or even separation between the mother and the child. There is the potential for impaired cognitive, physical, and psychological development of the child if the condition is not treated (Chandra et al., 2006; R. Kumar et al., 1995; Sit et al., 2006; Wisner et al., 1994). When given appropriate care, the impact on the child may be reduced (Murray, Cooper, & Hipwell, 2003). Identifying early symptoms and risk factors is therefore an important step to ensure appropriate care is given as early as possible.

Due to the severity of the symptoms, the risks of unsafe practices towards the baby, abusive incidents, or neglect can increase (Chandra et al., 2006). Although homicide rarely occurs, women do express more homicidal ideation than in other nonpsychotic childbirth onset illnesses such as postpartum depression (Sit et al., 2006; Wisner et al., 1994). Approximately 4% of women who suffer from postpartum psychosis commit neonaticide, often related to a denial of pregnancy, depersonalisation, dissociative hallucinations, or intermitted amnesia (M.G. Spinelli, 2001; M.G. Spinelli, 2009). Suicidal ideation is also associated with infanticidal ideas (Babu, Subbakrishna, & Chandra, 2008). Compared to healthy women, in women with postpartum psychosis the risk of suicide is increased 70-fold in the first

year after delivery, with depressive symptoms being the most important risk factor for suicidal ideation and attempts (Appleby, Mortensen, & Faragher, 1998; Babu et al., 2008; Brockington, 1996; Rohde & Marneros, 1993). In fact, the majority of maternal deaths with a psychiatric cause are due to suicide (up to 80%) and suicide accounts for 28% of maternal death in general (Lewis, 2007; M. Oates, 2003a, 2003b). Attempts are often aggressive and irreversible (e.g. jumping from heights, self-incineration) (Babu et al., 2008; M. Oates, 2003a, 2003b; Sit et al., 2006). In order to prevent these serious consequences it is important to identify and implement effective treatment to prevent or treat postpartum psychosis.

1.1.2.6 Treatment

As will be discussed in section 1.2.2, women with a diagnosis of bipolar disorder or schizoaffective disorder or those who have a history of psychoses unrelated to childbirth are at a high risk of developing postpartum psychosis. Pharmacological management does not only focus on the treatment of the condition but also on its prevention. If preventative treatment is started during pregnancy or breastfeeding it is important to balance benefits and possible side effects for mother and baby (Gentile, 2006; Price, Turnbull, Gregory, & Stevens, 1989). Possible pharmacological side effects include foetal abnormalities or a neurodevelopmental delay in the infant (Gentile, 2011). Mothers may experience more specific adverse reactions to medication during pregnancy, such as nausea, vomiting, and excessive weight gain, indirectly contributing to the occurrence of complications during pregnancy (Gentile, 2011). Currently, research results regarding treatment and prevention are inconclusive and many studies show limitations, such as small sample sizes, that make it difficult to draw conclusions about the effectiveness of the treatment and the severity of the side effects (Gentile, 2006, 2011).

In women at risk of postpartum psychosis due to a previous psychiatric diagnosis, lithium seems to be the first choice for prevention of postpartum psychosis starting during pregnancy (Doucet, Jones, Letourneau, Dennis, & Blackmore, 2011; Roy & Payne, 2009). Typical antipsychotics (e.g. haloperidol) have been shown to be relatively safe during pregnancy, as well as other psychotropic drugs including venlafaxine, bupropion, mirtazapine and tricyclic antidepressants (Roy & Payne,

2009). It has been found that lithium and other mood stabilisers, being used prophylactically, lead to significantly better outcomes in women at risk of postpartum psychosis, reducing the relapse rate enormously (ranging from 10% to 70%) (Austin, 1992; V. Bergink et al., 2012; Bilszta, Meyer, & Buist, 2010; L. S. Cohen, Sichel, Robertson, Heckscher, & Rosenbaum, 1995; Viguera et al., 2000).

The acute treatment of postpartum psychosis most commonly involves mood stabilisers, antipsychotics and benzodiazepines (L. S. Cohen et al., 1995; Sit et al., 2006; M.G. Spinelli, 2009). Due to the fact that postpartum psychosis is such a severe disorder, hospitalisation in a specialist psychiatric setting is frequently required (Sharma, 2008). Electroconvulsive therapy (ECT) is typically used for women resistant to pharmacotherapy (M.G. Spinelli, 2009). It has been recommended that ECT should be the treatment of choice in postpartum psychosis as it does not involve the potential detrimental side effects of pharmacological treatment on mother and baby, although more research is needed to confirm this idea (Doucet et al., 2011; Focht & Kellner, 2012).

In addition to the pharmacological management, it is also important to consider clinical interventions, such as help with parenting skills in order to meet the women's and children's needs (Doucet et al., 2011; Doucet, Letourneau, & Blackmore, 2012). Recovery may take up to one year, during which the patient must be adequately supported (Heron et al., 2012). If treated appropriately women show good future employment and adjustment rates (Marks, Wieck, Checkley, & Kumar, 1992; Robling, Paykel, Dunn, Abbott, & Katona, 2000; Videbech & Gouliaev, 1995). The earlier postpartum psychosis or the risk of developing postpartum psychosis can be recognised and treated, the better the outcome is for the woman. Therefore, it is of great importance to identify potential risk factors as well as correlates contributing to postpartum psychosis.

1.2 Relation to other mental disorders

One of the most prominent risk factors for postpartum psychosis is mental health history, in particular a diagnosis of bipolar or schizoaffective disorder, a history of psychosis or schizophrenia, or a personal or family history of postpartum psychosis. Therefore, the clinical classification of postpartum psychosis remains controversial

and the precise relationship of postpartum psychosis to other postpartum mood disorders and other mental disorders is still a matter of debate. In the following section this relationship will be discussed.

1.2.1 Relation to other postpartum mood disorders

While a wide variety of disorders can develop during the postpartum period, such as post-traumatic stress disorder, obsessive-compulsive disorder, and anxiety (I. Brockington, 2004; I. F. Brockington, 2004), the focus of this paragraph will be on postpartum mood disorders under which postpartum psychosis is typically classified. Postpartum mood disorders are classified into three categories: postpartum blues, postpartum depression, and postpartum psychosis (M. R. Oates, 2009; G. E. Robinson & Stewart, 1986). Postpartum blues, considered as a rather benign form of a postpartum mood disorder, often lasts only a few days and presents with crying and emotional lability or irritability and is usually manageable with emotional reassurance. Although postpartum blues can be distressing at the time, it has not been associated with recognised serious negative consequences on mother or baby (Chaudron & Pies, 2003; M.W. O'Hara, 2009).

Postpartum depression and postpartum psychosis are both considered as serious disorders which can have a severe impact on the life of mother and baby, including suicide and infanticide (Appleby et al., 1998; Chaudron & Pies, 2003; Doucet, Dennis, Letourneau, & Blackmore, 2009; M.G. Spinelli, 2001), although they differ in terms of their risk factors, presentation and management. Most experts agree that postpartum psychosis and postpartum depression are not distinct nosological entities (Doucet et al., 2009; Jones, 2010). Postpartum depression is diagnosed, similarly to postpartum psychosis, as a mood disorder with a postpartum onset specifier, in the DSM-IV with an onset within four weeks after childbirth and in the ICD-10 within six weeks after childbirth (American Psychiatric Association, 1994; World Health Organization, 1992). According to the DSM-IV, there must be a minimum of two weeks in which the patient presents with depressed mood or has a loss of interest or pleasure in daily activities that represents a change in the normal behaviour and causes impairment in everyday functioning. Additionally, at least five of these symptoms must also be present nearly every day: 1. depressed mood or irritable most

of the day; 2. decreased interest or pleasure in most activities, most of each day; 3. significant weight change or change in appetite; 4. insomnia or hypersomnia; 5. psychomotor agitation or retardation; 6. fatigue or loss of energy; 7. feelings of worthlessness or excessive or inappropriate guilt; 8. diminished ability to think or concentrate, or indecisiveness; 9. thoughts of death or suicide, or has suicide plan (American Psychiatric Association, 1994; Doucet et al., 2009). The new DSM-V criteria continue the use of four weeks into the postpartum period, however also cover the time during pregnancy (i.e. peripartum period), as episodes of depression commonly occur during pregnancy (Jones & Smith, 2009; M.W. O'Hara & McCabe, 2013).

Most studies report that postpartum depression is not distinctive to depression unrelated to childbirth in its symptomatology (Doucet et al., 2009; Jones, 2008, 2010; G. E. Robinson & Stewart, 1986), although there is some inconsistency in the literature.

As shown in Table 1.2, postpartum depression is more common than postpartum psychosis and shows a different symptom profile. Women with postpartum psychosis can be mainly differentiated from those with major depression by the presence of cognitive disturbances, hallucinations, delusional beliefs, and disorganised behaviour. However, as discussed in paragraph *1.1.2.4 Onset*, it has been found that mild hypomanic symptoms, which may be an early sign of the development of a postpartum psychotic episode (Heron et al., 2008), are also common among women who develop postpartum depression (Glover et al., 1994; Heron et al., 2005; Heron et al., 2009; Kendell, McGuire, et al., 1981). Because of the sudden onset, and the rapid deterioration that often follows, mothers presenting with postpartum psychosis tend to be admitted sooner following delivery than women with postpartum depression. It has been reported that as more time elapses after delivery, more women present with a non-psychotic form of illness (Lier, Kastrup, & Rafaelsen, 1989). In addition, postpartum depression has been reported to have a stronger association with stressful life events before symptom onset compared to postpartum psychosis (Brockington, Martin, Brown, Goldberg, & Margison, 1990; Doucet et al., 2009; R. Kumar et al., 1993; Marks et al., 1992). However, results are inconsistent and some authors suggest that stressful life events or social stressors (e.g. marital or socioeconomic status) do equally play a role in postpartum psychosis (Cheetham, Rzadkowolsk, &

Rataemane, 1981; Kendell et al., 1987; Kendell, Rennie, Clarke, & Dean, 1981; Nager, Johansson, & Sundquist, 2006; Robertson Blackmore et al., 2006). One major risk factor for a postpartum depression is a personal history of depression (Doucet et al., 2009), while for postpartum psychosis, having a history of bipolar disorder is one of the main risk factors, which will be discussed in the next section.

Table 1.2 Comparison of postpartum depression and psychosis

Postpartum Depression	Postpartum Psychosis
Prevalence	
13%-15%	0.1%-0.2%
Risk factors	
Personal history of depression	Personal/family history of postpartum psychosis
Depression/anxiety during pregnancy	Personal/family history of bipolar disorder
Family psychiatric history	Genetics
Hormonal changes	Hormonal changes
Life stress	Primiparity
Low social support	Sleep loss
Poor marital relationship	
Onset	
2 weeks to 1 year postpartum	Sudden, usually within 2 weeks postpartum
Symptoms	
Nonpsychotic depression	Manic or affective psychosis
Depressed mood	Mania
Loss of interest	Mood lability
Weight change	Delusions
Insomnia or hypersomnia	Hallucinations
Psychomotor agitation	Bizarre behaviour
Fatigue or loss of energy	Severe depression
Feelings of worthlessness or guilt	Confusion
Decreased concentration	Perplexity
Thoughts of death or suicide	
Management	
Nondirective counselling	Hospitalisation
Cognitive behavioural therapy	Mood stabilisers
Interpersonal psychotherapy	Antipsychotics
Psychodynamic therapy	Hormones
Telephone-based peer support	ECT
Antidepressants	Antidepressants (with caution)
Long-term outcomes	
25% have non-postpartum episodes	62% have non-postpartum episodes
41% have postpartum episodes	57% have postpartum episodes

Taken from Doucet et al., 2009

1.2.2 Relation to bipolar disorder and psychosis spectrum

Various studies have investigated the relationship between postpartum psychosis and other mental disorders in the bipolar disorder and psychosis spectrum and these are discussed in the following section. Confusion and disagreement over the clinical classification and the inadequacy of diagnostic tools have contributed to the

difficulties in studying this accurately (Chaudron & Pies, 2003). Therefore, the studies discussed here will be grouped according to the following three clusters:

- 1) Studies focusing on women with a current or previous episode of postpartum psychosis, investigating whether affective diagnoses or diagnoses in the psychosis domain are prevailing. Follow-ups of these studies are indicative of whether having a postpartum psychotic episode leads to a higher risk of developing further illness, related and unrelated to the puerperium. Studies comprising women suffering from an undefined severe postpartum illness are included in this cluster, as they typically involve women presenting with postpartum psychosis (see Table 1.3).
- 2) Studies focusing on women with a diagnosis of bipolar disorder. These studies are important in order to find out more about the risk of developing postpartum psychosis in the context of a diagnosis of bipolar disorder and vice versa (see Table 1.4).
- 3) Studies investigating women with a diagnosis within the psychosis spectrum. These studies can help to find out more about the risk of developing postpartum psychosis in the context of a diagnosis within the psychosis spectrum (see Table 1.5).

In all three tables, the country of the study, whether the study was based on medical records or on interviews, the diagnostic criteria used, the length of follow-up and the time of delivery will be reported when stated in the original study. Further, the sample size including the diagnostic distributions and relapses will be presented, as well as whether or not a control group was included.

Table 1.3 Studies assessing mothers with postpartum psychosis/severe postpartum disorders

Authors/ Year/ Country	Based on/ Admissions/ Follow-up	Diagnostic criteria/ Time after delivery	Sample size/ Diagnosis	Control Group	Subsequent episodes
Protheroe, 1969 UK	Medical records 1927-1961 1-35 years	Not reported (NR) 6 weeks	N=134 <i>91 mood disorder (19 mania, 72 depression) 37 schizophrenia 6 organic psychosis</i>	None	121 deliveries, 14 women had 18 postpartum episodes (PE) 40 women had non- postpartum episodes (NPE) 5 women had PE and NPE
Dean & Kendell, 1981 UK	Medical records 1971-1977 NR	Research Diagnostic Criteria (RDC) 3 months	N=71 <i>58 mood disorder (9 mania, 49 depression) 4 schizoaffective 1 schizophrenia 5 unspecified functional psychosis 3 other</i>	Diagnosis matched controls with NPE	NR
Brockington, 1981 UK	Interview, observation, & self-rating 1976-1979 NR	RDC 2 weeks	N=56 <i>39 mood disorder (17 mania, 22 depression) 12 schizoaffective 5 schizophrenia</i>	52 women with NPE <i>23 mood disorder (10 mania, 13 depression) 13 schizoaffective 16 schizophrenia</i>	NR
Katona, 1982 UK	Medical records 1970-1980 NR	DSM-III 6 months	N=84 <i>71 mood disorder (18 mania, 53 depression) Other diagnoses not applicable to DSM</i>	Diagnosis matched controls with NPE	NR
Hays & Douglass, 1984 Canada	Medical records and personal investigation 1963-1975 Mean 5 years	DSM-III 10 days	N=9 <i>9 schizophrenia</i>	10 patients with schizophreniform variant of bipolar disorder	NR

Authors/ Year/ Country	Based on/ Admissions/ Follow-up	Diagnostic criteria/ Time after delivery	Sample size/ Diagnosis	Control Group	Subsequent episodes
Schoepf et al., 1984 Switzerland	Medical records and interview 1958-1977 5-24 years	RDC 3 months	N=57 <i>43 mood disorder (20 depression, 13 mania and 10 depression with psychotic symptoms) 14 Psychoses</i>	None	32 deliveries, 11 women had PE 37 had NPE
Davidson & Robertson, 1985 UK	Medical records and interview 1946-1971 1-32 years	NR 3 months	N=82 <i>58 mood disorder (15 bipolar, 43 depression) 13 schizophrenia 11 other</i>	None	19 women had PE 39 had NPE
Meltzer & Kumar, 1985 UK	Medical records 1979-1980 NR	RDC 1 year	N=142 <i>97 mood disorder (31 mania, 3 bipolar, 63 depression) 8 schizoaffective 9 schizophrenia 3 unspecified functional psychosis 25 other</i>	None	NR
Platz & Kendell, 1988 UK	Medical records and interview 1971-1980 Mean 9 years	RDC 3 months	N=72 <i>66 mood disorder (12, mania, 54 depression) 6 schizoaffective</i>	Diagnosis matched controls with NPE	40 deliveries (sample), 4 PE 41 deliveries (controls), 4 PE Controls had more NPE
Dean et al., 1989 UK	Medical records and interview 1971-1981 NR	ICD-8,-9 RDC	N=51	33 women with PE and NPE (mood) 19 women with NPE (mood)	36% and 50% of deliveries followed by PE in sample and mixed control group respectively

Authors/ Year/ Country	Based on/ Admissions/ Follow-up	Diagnostic criteria/ Time after delivery	Sample size/ Diagnosis	Control Group	Subsequent episodes
Agrawal et al., 1990 India	Interview NR NR	RDC 3 months	N=144 36 mood disorders (4 mania, 32 depression) 8 schizoaffective 32 schizophrenia 68 unspecified functional psychosis	Diagnosis matched controls with NPE	12 women with past history of postpartum psychosis (8 schizophrenia, 2 mania, 2 schizomania) and 6 with schizophrenia
Klompenhouwer & van Hulst, 1991 Netherlands	Medical records 1967-1989 NR	RDC 3 months	N=250 71 mood disorder (29 mania , 2 bipolar, 40 depression) 63 schizoaffective 12 schizophrenia 74 unspecified functional psychosis 30 others	None	NR
Benvenuti et al., 1992 Italy	Medical records and interview 1973-1987 4-18 years	DSM-III-R 8 weeks	N=30 25 mood disorder (14 bipolar, 1 mania, 10 depression) 2 schizoaffective 3 brief reactive psychosis	None	8 deliveries, 4 women had 5 PE 19 women had NPE
Rohde & Marneros, 1993 Germany	Interview 1950-1979 12-41 Years	DSM- III & III-R 6 weeks	N=61 8 affective disorder 30 schizoaffective 17 schizophrenia 6 organic mental disorder	None	46 deliveries, 8 women had 8 PE 39 women had NPE
Kumar et al., 1995 UK	Medical records 1988-1989 NR	RDC NR 2 weeks	N=100 38 mood disorder (17 mania, 15 bipolar, 7 depression (psychotic)) 18 schizoaffective 20 schizophrenia 24 non-psychotic disorders	None	NR

Authors/ Year/ Country	Based on/ Admissions/ Follow-up	Diagnostic criteria/ Time after delivery	Sample size/ Diagnosis	Control Group	Subsequent episodes
Videbech & Gouliaev, 1995 Denmark	Medical records and interview (general practitioner) 1973-1980 7-14 years	ICD-8/ DSM-IV 1 year	N=50 (first onset) <i>38 mood disorders (6 mania, 3 mixed mania, 29 depression) 6 schizophreniform psychosis 5 schizophrenia 1 brief reactive psychosis</i>	Matched healthy controls	16 women with delivery, 4 women had PE 30 women had NPE
Kirpinar et al., 1999 Turkey	Medical records and interview 1973-1994 2-23 years	DSM-IV 3 months	N=64 (first onset) <i>25 mood disorder (11 mania, 14 depression) 19 schizophreniform 20 brief psychotic disorder</i>	64 matched controls with NPE (psychosis)	52 women had NPE <i>11 bipolar 7 depressive 7 schizoaffective 27 schizophrenia</i>
Pfuhmann et al., 1999 Germany	Medical records and interview 1981-1990 6-26 years	ICD-10/ Leonhard's classification 6 months	N=39 (first onset) <i>16 mood disorder (5 bipolar, 11 depression) 5 schizoaffective 5 schizophrenia 8 acute polymorphous psychotic disorder 5 other</i>	None	22 deliveries, 9 women developed 11 PE 20 women developed NPE
Robling et al., 2000 UK	Medical records and interview (follow-up Katona, 1982) 1970-1980 17-28 years	ICD-10 6 months	N=64 <i>54 mood disorders (17 mania, 2 bipolar, 35 depression) 2 schizoaffective 3 schizophrenia 2 other psychoses 3 other</i>	None	34 deliveries with 10 women (29%) developing PE 48 women had NPE

Authors/ Year/ Country	Based on/ Admissions/ Follow-up	Diagnostic criteria/ Time after delivery	Sample size/ Diagnosis	Control Group	Subsequent episodes
Garfield et al., 2003 UK	Medical records and interview 1981-1985 7-12 years	RDC 6 months	N=69 <i>36 mood disorder (12 mania, 24 depression) 11 schizoaffective 13 schizophrenia 2 unspecified functional psychosis 7 other</i>	None	27 deliveries, 14 PE, Recurrence rate higher for psychoses than depression (80 versus 27%) 41 women had NPE (out of 47 traced)
Robertson et al., 2005 UK	Medical records and interview NR 0.5-33 years	DSM-IV 4 weeks	N=103 <i>90 bipolar 13 schizoaffective</i>	None	54 women had another delivery, 31 women had PE 64 experienced NPE (mood)
Kisa et al., 2007 Turkey	Interview 1998-2006 min. 2 years	DSM-IV 6 months	N=23 <i>5 bipolar 4 schizoaffective 4 schizophreniform 6 schizophrenia 4 brief psychotic disorder</i>	25 matched controls with first onset NPE	11 women had another delivery, 7 women had PE 15 women had NPE
Bergink et al., 2011 Netherlands	Interview and questionnaire 2005-2009 NR	DSM-IV 4 weeks	N=51 (first onset) <i>32 with manic psychotic features 4 with only psychotic features 7 with depressed psychotic features 8 with mixed features</i>	Population based control group of 6969 women (2 months follow-up)	NR
Nager et al., 2012 Sweden	Medical records 1975-2004 1-30 years	ICD-8,-9,-10 3 months	N=1340 <i>130 mothers with schizophrenia 260 with affective psychosis 950 with unspecified psychosis</i>	None	High lifelong NPE rate, Schizophrenia incidence (0.64) affective psychosis (0.42) unspecified psychosis (0.3)

Table 1.3 Studies investigating the relationship between postpartum psychosis, bipolar disorder and psychoses unrelated to childbirth. NR=Not reported. RDC=Research Diagnostic Criteria. ICD=International Classification of Diseases. DSM=Diagnostic and Statistical Manual of Mental Disorders. PE= Postpartum episodes. NPE=Non-postpartum episodes.

Table 1.4 Studies assessing mothers with bipolar disorder

Authors/ Year/ Country	Based on/ Admissions/ Follow-up	Diagnostic criteria/ Time after delivery	Sample size/ Diagnosis	Control Group	Subsequent episodes
Bratfos & Haug, 1966 Norway	Medical records & personal investigation 1952-1961 2-11 years	NR 3 months	N=82	None	251 deliveries of 82 women, 31 women developed 52 PE (all depressive polarity)
Reich & Winokur, 1970 US	Interview 1964-1967 NR	NR 6 months	N=20	None	46 deliveries, 8 women developed 14 PE (11 manic polarity)
Kendell et al., 1987 UK	Medical records 1970-1981 NR	ICD-9/ RDC 3 months	N=33	22 mothers with schizophrenia 79 mothers with depressive neurosis	44 deliveries (sample), 7 PE 132 deliveries (controls), 3 PE
Hunt & Silverstone, 1995 UK	Medical records & interview NR 2-5 years	RDC 3 months	N=23	None	42 deliveries, 22 PE
Jones & Craddock, 2001 UK	Medical records & interview NR	DSM-IV 6 weeks	N=152 (also schizoaffective)	None	313 deliveries, 58 women developed 81 PE 39 women developed mood episodes in pregnancy or 6 months postpartum
Serretti et al., 2006 Italy	Medical records & interview 1990-2000 NR	DSM-III-R & IV 4 weeks	N=22 (postpartum onset)	101 women with bipolar disorder non-postpartum onset	Women with PE had fewer recurrences compared to controls
Munk-Olsen et al., 2009 Denmark	Medical records 1973-2005 NR	ICD-8 & 10 1 year	N=208	878 mothers with schizophrenia-like disorders	56 women (27%) developed PE (sample) 138 women (16%) developed PE (controls)

Authors/ Year/ Country	Based on/ Admissions/ Follow-up	Diagnostic criteria/ Time after delivery	Sample size/ <i>Diagnosis</i>	Control Group	Subsequent episodes
Munk-Olsen et al., 2012 Denmark	Medical records 1970-2006 NR	ICD-8 & 10 1 year	N=132 (postpartum onset)	2930 women with bipolar disorder non-postpartum onset	19 (14%) women with postpartum and 119 (4%) women with non-postpartum onset developed bipolar disorder within 15 years

Table 1.4. Studies investigating the relationship between postpartum psychosis, bipolar disorder and psychoses unrelated to childbirth. NR=Not reported. RDC=Research Diagnostic Criteria. ICD=International Classification of Diseases. DSM=Diagnostic and Statistical Manual of Mental Disorders. PE= Postpartum episodes. NPE=Non-postpartum episodes.

Table 1.5 Studies assessing women with previous psychoses

Authors/ Year/ Country	Based on/ Admissions/ Follow-up	Diagnostic criteria/ Time after delivery	Sample/ <i>Diagnosis</i>	Control Group	Subsequent episodes
McNeil, 1988a, 1988b, 1986 Sweden	Interview 1973-1977 Min. 2 years	RDC 6 months	N=88 <i>15 affective illness</i> <i>15 cycloid psychosis</i> <i>17 schizophrenia</i> <i>6 psychogenic psychosis</i> <i>18 postpartum psychosis</i> <i>17 other psychosis</i>	104 healthy controls	25 women had PE
Harlow et al., 2007 Sweden	Medical records 1987-2001 NR	ICD-8, -9, - 10 3 months	N=1348 <i>276 schizophrenia</i> <i>46 schizoaffective</i> <i>1026 non-affective psychotic disorder</i>	786 women with bipolar disorder	Sample: 14.54% risk of developing PE (psychosis) and 2.59% PE (mood) Controls: 1.35% risk of developing PE (psychosis) and 8.46% PE (mood)

Table 1.5. Studies investigating the relationship between postpartum psychosis, bipolar disorder and psychoses unrelated to childbirth. NR=Not reported. RDC=Research Diagnostic Criteria. ICD=International Classification of Diseases. DSM=Diagnostic and Statistical Manual of Mental Disorders. PE= Postpartum episodes. NPE=Non-postpartum episodes.

The studies reviewed in Tables 1.3, 1.4, and 1.5 show that the existing research on postpartum psychosis is limited and inconsistent. There are discrepancies concerning the diagnostic criteria used and there is no consensus on the time-frame within which women can be included in the study, ranging from two weeks to up to a year across studies. Many studies are exclusively based on medical records and lack verification by a structured clinical interview. This is a particular concern when the diagnosis in the records was obtained some decades ago, when the diagnostic criteria were likely to be different. This is an issue that will lead to inconsistencies in the data and reduce comparability across studies. The time-frame of follow-up also differed greatly, potentially contributing to different percentages of relapses within the follow-up period. Finally, many studies did not use a control group and only 11 of the 34 studies published information on the psychiatric family history. This information is important in order to compare similarities between postpartum psychosis and mood disorders or psychoses unrelated to childbirth. It will be important for future studies to develop more agreement on the diagnostic criteria and onset time-frame in order to investigate specific questions regarding postpartum psychosis. Based on the literature there seem to be at least three possible approaches to the classification of postpartum psychosis (McGorry & Connell, 1990):

1. Postpartum psychosis as part of the bipolar spectrum.
2. Postpartum psychosis as a separate diagnostic entity.
3. Postpartum psychosis as part of the psychosis spectrum.

1.2.2.1 Postpartum psychosis as part of the bipolar spectrum

Many studies presented in this literature review support the view that postpartum psychosis fits best as part of the bipolar disorder spectrum. The key evidence supporting this position is that having a diagnosis of bipolar disorder puts a woman at higher risk of developing a postpartum psychotic episode after delivery (i.e. a 30-50% higher risk compared to healthy controls) (Jones & Craddock, 2001; Robertson, Jones, Haque, Holder, & Craddock, 2005). Some authors suggest, however, that pregnancy itself might have a protective effect for women with a bipolar disorder as there are typically fewer and shorter relapses during pregnancy than either before or

after (Grof et al., 2000). Women with bipolar disorder *and* a first-degree relative with postpartum psychosis have a 74% chance of developing postpartum psychosis compared to 30% chance when no history of postpartum psychosis is present in the family (Jones & Craddock, 2001). This demonstrates that hereditary factors are also implicated in susceptibility to puerperal psychosis in women with bipolar disorder (Jones & Craddock, 2001). Other studies support the finding that the risk of developing postpartum psychosis is higher in women with a first-degree relative with postpartum psychosis, suggesting that familial factors are indeed involved (Craddock et al., 1994; Kane, 1968; Reich & Winokur, 1970; Thuwe, 1974; Whalley, Roberts, Wentzel, & Wright, 1982). The morbidity risk for first-degree relatives of women with postpartum psychosis has been found to be high overall and similar to that of women with non-postpartum mood disorder or also schizophrenia, suggesting a close relationship between postpartum psychosis and other mental disorders (P. Agrawal et al., 1990; Benvenuti et al., 1992; Dean, Williams, & Brockington, 1989; Kirpinar, Coşkun, Cayköylü, Anaç, & Ozer, 1999; Platz & Kendell, 1988; Protheroe, 1969). A shorter time to non-postpartum relapses is also associated with a positive family history of mental illness (Robertson et al., 2005).

In addition, it was also found that a first episode of postpartum psychosis significantly predicted later conversion to bipolar disorder. Percentage of conversion has been reported to be 14% (compared to 4% of women with a non-postpartum onset) within 15 years and is even higher over the life-time (Brockington, 1996; Munk-Olsen, Laursen, Meltzer-Brody, Mortensen, & Jones, 2012; Sit et al., 2006). Some studies report that there are no noticeable differences concerning the symptomatology between postpartum and non-postpartum episodes (Brockington et al., 1981; Reich & Winokur, 1970). Others find differences in onset and symptoms between women with postpartum onset and women with previous bipolar disorder (see section 1.2.2.2) (V. Bergink, Lambregtse-van den Berg, Koorengel, Kupka, & Kushner, 2011). Cases with exclusive postpartum psychosis are rare and affective symptoms seem to be more common than psychotic symptoms (Brockington et al., 1981; Reich & Winokur, 1970; Videbech & Gouliaev, 1995). This points towards a close association between postpartum psychosis and bipolar disorder, indicating that postpartum psychosis likely presents as an episode of bipolar disorder triggered by childbirth or that it at least belongs to a possible heterogeneous bipolar disorder

group instead of representing a separate entity (Benvenuti et al., 1992; Bratfos & Haug, 1966; Brockington et al., 1981; Davidson & Robertson, 1985; Dean & Kendell, 1981; Hunt & Silverstone, 1995; Jones & Craddock, 2001; C. L. Katona, 1982; Kendell et al., 1987; Meltzer & Kumar, 1985; Munk-Olsen et al., 2012; Munk-Olsen et al., 2009; Platz & Kendell, 1988; Protheroe, 1969; Reich & Winokur, 1970; Robertson et al., 2005; Robling et al., 2000; Videbech & Gouliaev, 1995).

1.2.2.2 Postpartum psychosis as a diagnostic entity

An alternative approach is to consider postpartum psychosis as a separate diagnostic entity. Support for this view comes from studies assessing differences in symptoms, illness course and family background between women with a postpartum and non-postpartum episode. Some studies find differences in symptoms and also in the progression of the disorder between women with postpartum and non-postpartum onset (Dean & Kendell, 1981; Hunt & Silverstone, 1995). Women with a postpartum onset appear to have more Schneiderian first rank symptoms (e.g. thought broadcasting, experience of alienation, experiences of influence, and auditory hallucinations) and fewer first-degree relatives with an affective disorder (Hays, 1978; Hays & Douglass, 1984; Kadrmas et al., 1979), more cognitive disorganisation, bizarre behaviour, thought disorganisation, lack of insight, and delusions of reference or persecution related to childbirth (e.g. about the identification of the baby) compared to those with non-postpartum episodes (M.G. Spinelli, 2009; Wisner et al., 1994).

With one exception, a postpartum onset has been associated with better illness outcome than a non-postpartum onset (i.e. fewer non-postpartum recurrences than with a non-postpartum onset) (Davidson & Robertson, 1985; Hunt & Silverstone, 1995; C. L. Katona, 1982; Platz & Kendell, 1988). In fact, women with postpartum psychosis seem to have a better prognosis in terms of number of relapses, time on medication, and employment and social functioning than women who had also or only non-postpartum episodes or schizophrenia (Davidson & Robertson, 1985; Dean et al., 1989; Doucet et al., 2009; Nager, Johansson, & Sundquist, 2005; Serretti, Olgiati, & Colombo, 2006). Before symptom onset, women have often attained higher functional levels compared to those with a chronic illness (Sit et al., 2006).

This evidence comes together to show that postpartum psychosis and psychoses unrelated to childbirth are not equivalent. However, none of these studies exclude the possibility that despite differences in symptomatology and progression, postpartum psychosis might be a separate entity within an affective or psychotic disorder spectrum, demonstrating the potential heterogeneity of these spectra.

1.2.2.3 Postpartum psychosis as part of the psychosis spectrum

A third approach suggests that postpartum psychosis could be part of the psychosis spectrum. A few studies have found a predominance of diagnoses within the psychoses rather than the affective spectrum among women suffering from postpartum psychosis (P. Agrawal et al., 1990; Garfield, Kent, Paykel, Creighton, & Jacobson, 2004; Harlow et al., 2007; Kirpinar et al., 1999; Kisa et al., 2007; Klompenhouwer & van Hulst, 1991; McNeil, 1986, 1988a, 1988b; Nager et al., 2012; Pfuhlmann, Franzek, Beckmann, & Stöber, 1999; Schöpf, Bryois, Jonquière, & Le, 1984). As with bipolar disorder, it has been found that the risk of postpartum psychosis is higher in women with a personal or family history of psychoses unrelated to childbirth (Schöpf et al., 1984). However, childbirth may have a smaller effect on severe illness courses of schizophrenia, as benign forms of schizophrenia or other psychoses have been found to be more influenced by childbirth (Davies, McIvor, & Channi, 1995).

1.2.2.3.1 Postpartum psychosis and schizoaffective disorder

One nosological category that is particularly interesting in relation to the risk of postpartum psychosis is “schizoaffective disorder”. There has been in fact extensive debate as to whether this diagnosis simply reflects the co-occurrence of both schizophrenia and a mood disorder (bipolar disorder or major depressive disorder), or whether is a variant of schizophrenia in which mood symptoms like irritability, elation, sadness, are particularly prominent, or whether actually this condition reflects severe forms of affective disorders that do not completely remit between mood episodes. In any case, it is accepted that the phenomenology of this disorder is characterised by the presence of important affective symptoms. Considering the particularly strong relationship between risk of postpartum psychosis and bipolar

affective disorder described above, it is therefore important to consider the relationship with this diagnosis more closely.

According to the DSM-IV, schizoaffective Disorders are classified under schizophrenia and other psychotic disorders (American Psychiatric Association, 1994). The DSM-IV criteria for schizoaffective disorder include: A. an uninterrupted period of illness during which, at some time, there is either a major depressive episode, a manic episode, or a mixed episode concurrent with symptoms that meet symptom criteria for schizophrenia; b. during the same period of illness, there have been delusions or hallucinations for at least two weeks in the absence of prominent mood symptoms; C. symptoms that meet criteria for a mood episode are present for a substantial portion of the total duration of the active and residual periods of the illness. The DSM-IV further differentiates two types of schizoaffective disorder. The bipolar type is diagnosed if the disturbance includes a manic or a mixed episode (or a manic or a mixed episode and major depressive episodes). The depressive type is diagnosed if the disturbance only includes major depressive episodes (American Psychiatric Association, 1994).

As discussed in the previous section, women diagnosed with schizophrenia and other psychoses are also considered at higher risk of developing psychosis after childbirth (Schöpf et al., 1984). However, the term postpartum psychosis often refers to the acute onset of an episode of severe affective psychosis, including manic, depressed and schizoaffective forms in a woman who has been well before delivery (independently of a previous psychiatric history) (Jones & Smith, 2009). In the literature, a high risk to develop postpartum psychosis due to a diagnosis of schizoaffective disorder bipolar type is typically rated similarly to the estimated risk due to having a previous bipolar disorder diagnosis and therefore higher than that conferred by a schizophrenia diagnosis (Brockington, 1996; Dean et al., 1989; Jones & Craddock, 2001; Robertson et al., 2005; Robling et al., 2000; Sit et al., 2006). Most research studies conducted by experts in field, thus, include women with bipolar disorder as well as schizoaffective disorder bipolar type among their recruitment criteria (Jones et al., 2007; Robertson Blackmore et al., 2006; Robertson, Jones, Middle, Moray, & Craddock, 2003). This may be particularly relevant in studies investigating the neurobehavioral dysfunctions present in these diagnostic categories, which would be better conceptualised as lying along a continuum rather

than boxed into separate nosological categories. For further discussion of the recruitment strategy in this study please see paragraph *1.2.4 Summary*. It is important to note that there are differences between Western and non-Western cultures concerning the rates of diagnosis of schizophrenia and other psychoses and mood disorders following postpartum psychosis (Sit et al., 2006).

1.2.2.3.2 Cross cultural comparison

Postpartum psychosis has a similar incidence worldwide (P. Agrawal et al., 1990; Cheetham et al., 1981; Ifabumuyi & Akindele, 1985; R. Kumar, 1994; Makanjuola, 1982; Rahim & Al-Sabiae, 1991; Shoeb & Hassan, 1990). Studies conducted in India and Africa consistently find that more women with postpartum psychosis are diagnosed with schizophrenia compared to studies conducted in Western cultures (R. Kumar, 1994). This might imply a difference in the presentation of postpartum psychosis in other cultures, where women may show less affective and more psychotic symptoms, such as confusion (Kirpinar et al., 1999). Differences in diagnostic criteria are also a likely explanation, as a direct comparison between women hospitalised for postpartum psychosis in Saudi Arabia and the United Kingdom showed that women presented mainly with affective symptoms in both countries when the same criteria were used (Rahim & Al-Sabiae, 1991). This finding supports the view that postpartum psychosis is part of the bipolar disorder spectrum and that inconsistencies may be due to differences in the diagnostic criteria used in different settings.

1.2.3 Comparison to other high risk approaches

Investigating people at high risk of developing a specific disorder has become a common approach in both the bipolar disorder and psychosis research, as it offers the chance of early intervention, possibly postponing, ameliorating or preventing the onset of a disorder (McGuire, Selvaraj, & Howes, 2011; Yung et al., 2005). Furthermore, this approach provides the opportunity to study the illness from the very early stages, before other potential confounders, such as medication, institutionalisation, exposure to substance use, have altered the trajectory and the environmental and biological correlates of the disorder.

As discussed in the section 1.2.2 Relation to bipolar disorder and psychosis spectrum, women with a diagnosis of bipolar or schizoaffective disorder, and to a lesser degree psychosis unrelated to childbirth, are a group at a higher risk to develop postpartum psychosis compared to healthy controls (Jones & Craddock, 2001; Robertson et al., 2005; Sit et al., 2006). Therefore, investigating risk factors and correlates in this population differs from other high risk approaches in psychosis and bipolar disorder research. There, conceptually, the increased high risk is not conferred by a pre-existing diagnosis, but rather defined by the presence of a “genetic risk” or a “clinical risk” (Smieskova et al., 2013). For example, an individual at genetic high risk of bipolar disorder or psychosis would be someone who does not have these disorders but has a monozygotic twin or a first- or second-degree relative suffering from bipolar disorder or psychosis, respectively (Baig et al., 2010; Ettinger et al., 2012; Fusar-Poli, Howes, Bechdolf, & Borgwardt, 2012; Smieskova et al., 2013). Someone at clinical high risk of psychosis would be defined by the presence of a set of clinical -prodromal- symptoms, used to indicate a so called “at-risk mental state” (ARMS) (Aiello, Horowitz, Hepgul, Pariente, & Mondelli, 2012; Riecher-Rössler et al., 2007; Smieskova et al., 2013).

The at risk approach for postpartum psychosis is also different from other at risk approaches in that the conversion rate for the women at risk is very high, ranging from 30-50% after each delivery and even up to 75% if there is additionally a first-degree family history (Jones & Craddock, 2001; Robertson et al., 2005). Conversion rates for people at genetic or clinical risk of bipolar disorder or psychosis are typically lower. Studies report that conversion rates range from 13% to 30% within one year of follow up in psychosis studies (R. E. Carrión, McLaughlin, Goldberg, & et al., 2013; Haroun, Dunn, Haroun, & Cadenhead, 2006; McGuire et al., 2011) and from 15% to 30% over a lifetime in people at risk of bipolar disorder (Fusar-Poli et al., 2012). Furthermore, postpartum psychosis is associated with a discrete biological event, childbirth. This disorder has been reported to develop suddenly within the first days after childbirth, with 50% of women having a symptom onset in the first three days postpartum (Brockington, 1996; Heron et al., 2007; Sit et al., 2006). In contrast, people at genetic or clinical risk are often being followed up and monitored for years for the conversion to occur, and show a much slower conversion even when

this occurs (R. E. Carrión et al., 2013; Haroun et al., 2006; McGuire et al., 2011; Yung et al., 2005). Therefore, despite the nosological and practical difficulties in investigating postpartum psychosis, since the time of maximum risk in women at risk of postpartum psychosis is so well identifiable, research in this area also offers important advantages over other at risk approaches.

1.2.4 Summary

While some studies show that women with a diagnosis within the psychosis spectrum are at higher risk of developing postpartum psychosis and vice versa, postpartum psychosis seems to have a closer association with bipolar disorder (Jones & Smith, 2009). The mixed findings across studies are likely to be explained by differences in diagnostic criteria, time-frame, source of data and other methodological details. Whether postpartum psychosis is a separate diagnostic category or an exacerbation of an affective or psychotic disorder remains a matter of debate in the psychiatric literature. Some authors propose that it would be better to create a separate nosological entity as this might aid research, help to define treatment, and reduce the stigma associated with bipolar disorder and psychoses unrelated to childbirth (Boyce & Barriball, 2010). Nonetheless, the evidence suggests that postpartum psychosis is part of a lifelong non-specific affective disorder (Garfield et al., 2004; Nager et al., 2012; Pfuhmann, Stoeber, & Beckmann, 2002; Rohde & Marneros, 1993).

In order to create a homogenous group, based on the literature, specifically on studies led by Ian Jones, the focus of the research in this PhD is on women with diagnoses of bipolar or schizoaffective disorder (bipolar type) or with a personal or family history of postpartum psychosis. In addition to existing psychiatric diagnoses, other risk factors are likely to contribute to the development of postpartum psychosis and these will be explored in the following section together with potential correlates of postpartum psychosis.

1.3 Correlates

In the following section, biological, clinical, cognitive, emotional and neuroimaging findings in postpartum psychosis will be reviewed. Given the lack of research on

postpartum psychosis, evidence for potential cognitive, emotional and neuroimaging alterations will be reviewed in the light of related mental disorders.

1.3.1 Biological correlates

Here, findings in the hormonal domain as well as on the role of neurotransmitter and genes will be discussed.

1.3.1.1 Oestrogens

Although evidence suggests that levels of circulating gonadal steroid hormones in women with postpartum psychosis are normal (Wisner & Stowe, 1997), one theory proposes that postpartum psychosis is triggered by abrupt changes in oestrogen levels following delivery in women with a pre-existing vulnerability (Brockington, 1996; Wieck, 2011). At the end of pregnancy, serum oestrogen levels are very high, but decline abruptly after delivery (Hendrick, Altshuler, & Suri, 1998). Therefore, postpartum oestrogen deficiency can be severe and prolonged and can impact on the mood of the mother (Hendrick et al., 1998). Oestrogens have been suggested to be a protective factor, delaying or preventing the onset of psychoses, while low oestrogen levels are thought to put women at higher risk of developing a psychotic disorder (Cyr, Calon, Morissette, & Di Paolo, 2002; Wieck, 2011). The effects of oestrogens are also of interest in the context of the menstrual cycle and menstrual cycle related mood disorders, which are further discussed in paragraph 1.3.1.3. Menstrual cycle effects as the onset of psychotic symptoms has been associated with the low levels of oestrogens (I. F. Brockington, 2004; Brockington, Kelly, Hall, & Deakin, 1988; Brockington & Meakin, 1994; Huber, Borsutzky, Schneider, & Emrich, 2004).

If oestrogens are implicated in postpartum psychosis, their administration could potentially be useful in the prevention or treatment of this disorder. A number of studies have been carried out to investigate this therapeutic potential of oestrogens in postpartum psychosis. In a pilot study, the effect of daily oestrogens administration immediately after delivery as a prophylactic agent was investigated (Sichel, Cohen, Robertson, Ruttenger, & Rosenbaum, 1995). Seven women at risk of postpartum psychosis received oestrogens for four weeks. The study found that the administration prevented a relapse in all but one woman (Sichel et al., 1995). In two

studies, each using a sample size of two women with postpartum psychosis, oestradiol administered after more than eight weeks was also found to be effective in treating postpartum psychosis (Ahokas & Aito, 1999; Ahokas, Aito, & Turtiainen, 2000). In these studies, women showed a low pre-treatment oestradiol concentration and the rise in serum oestradiol during treatment coincided with a decline in psychotic symptoms, while the discontinuation of treatment resulted in a rebound of florid psychotic symptoms (Ahokas & Aito, 1999; Ahokas, Aito, & Turtiainen, 2000). Another study, assessing the effects of a 10 week course of sublingual oestradiol in 10 women who had developed postpartum psychosis, found that symptoms decreased as serum oestradiol levels increased (Ahokas, Aito, & Rimón, 2000). In addition, one patient who discontinued the therapy experienced a relapse (Ahokas, Aito, & Rimón, 2000).

Despite the evidence from four studies with a total of 21 participants, other work has suggested that administration of oestrogen is not preventative for postpartum psychosis. One study with a larger sample size of 29 pregnant women with a history of bipolar or schizoaffective disorder showed that relapse could not be prevented by the administration of oestradiol within 48 hours after delivery (C. Kumar et al., 2003). The fact that the study with the largest sample size shows no beneficial effect of oestrogens on the prevention of postpartum psychosis questions earlier results. Although it seems plausible that oestrogens are implicated in triggering postpartum psychosis, future studies will need to confirm the contribution of hormones to the development of postpartum psychosis. Another hormone that has been implicated in postpartum psychosis is cortisol.

1.3.1.2 Cortisol

Hypothalamic-pituitary-adrenal (HPA) axis activity is triggered by the release of corticotropin releasing hormone (CRH) and of vasopressin (AVP), synthesised in the hypothalamus, which in turn activates the secretion of the adrenocorticotrophic hormone (ACTH) from the pituitary (Borges, Gayer-Anderson, & Mondelli, 2013; Pariante & Lightman, 2008). ACTH then stimulates the secretion of glucocorticoids (i.e. cortisol in humans) from the adrenal cortex, which interacts with receptors in

multiple target tissues and is responsible for feedback inhibition to the hypothalamus and the pituitary (Borges et al., 2013; Pariante & Lightman, 2008).

High cortisol release is associated with stress (e.g. stressful life events such as childhood trauma) and has been documented in other mental health disorders such as depression and psychoses unrelated to childbirth (Aiello et al., 2012; Bennett & Maxwell, 2008; Schäfer & Fisher, 2011). Differences in cortisol levels have also been associated with the menstrual cycle and impaired neurocognitive functioning. A greater response to CRH stimulation linked to lower baseline cortisol levels was found in women with menstrual cycle related disorders compared to healthy controls and the luteal phase has been associated with low cortisol levels and neurocognitive impairment (Rubinow & Schmidt, 1995; Symonds, Gallagher, Thompson, & Young, 2004). For further discussion see paragraph 1.3.1.3 Menstrual cycle effects.

High cortisol levels are also associated with delivery (Hendrick et al., 1998) and have been associated with postpartum psychosis (Paykel, del Campo, White, & Horton, 1991). Using the dexamethasone suppression test of cortisol (i.e. by providing negative feedback to the pituitary gland via the synthetic glucocorticoid dexamethasone), elevated post-dexamethasone cortisol levels were found in women with postpartum psychosis compared to healthy controls (Paykel et al., 1991). These results are similar to those found in depression and indicate hormonal abnormalities in postpartum psychosis (Paykel et al., 1991). This finding suggests that it could be of importance in future studies to investigate the influence of cortisol levels, both during pregnancy and after delivery, on the development of postpartum psychosis.

1.3.1.3 Menstrual cycle effects

A proposed hormonal aetiology of postpartum psychosis would be supported by findings in the context of menstrual cycle effects (Brockington, 1996; Brockington & Meakin, 1994; Rubinow & Schmidt, 1995). The onset of psychotic symptoms has been associated with the low oestrogen/high progesterone phase of the cycle, the time preceding menstruation (i.e. pre-menstrual or luteal phase) (I. F. Brockington, 2004; I. F. Brockington et al., 1988; Brockington & Meakin, 1994). Women suffering from psychosis have also been found to be more likely to be admitted

during the luteal phase of their cycle (Huber et al., 2004). In addition, these women often show markedly reduced oestradiol levels and variability over the menstrual cycle compared to healthy controls and women suffering from other psychiatric disorders (Huber et al., 2004).

Rubinow and Schmidt (1995) reviewed the neuroendocrinological effects of the menstrual cycle on patients with menstrual cycle related disorders, referring to a group of disorders with a cyclic recurrence of mood and behavioural symptoms during the luteal phase of the menstrual cycle. According to their review, women with menstrual cycle related disorders, or the more general premenstrual syndrome, do not show abnormal circulating levels of gonatropins, gonadal steroids and their metabolites or hypothalamic-pituitary-ovarian axis function (Rubinow & Schmidt, 1995). These findings are similar to the above cited evidence, that levels of circulating gonadal steroid hormones in women with postpartum psychosis also seem to be normal (Wisner & Stowe, 1997). Nevertheless, these authors found that cyclic mood disturbances could be prevented in patients with menstrual cycle related disorders by ovarian suppression, and again be precipitated by administering oestrogens and progesterone (Rubinow & Schmidt, 1995).

An abnormal thyroid function and menstrual-cycle-independent differences in response to thyroid-releasing hormones have been found in women with premenstrual syndrome compared to healthy controls (Rubinow & Schmidt, 1995). Although differences in cortisol levels related to the luteal phase have not been consistently observed in women with menstrual cycle related disorders, or the more general premenstrual syndrome, there seem to be menstrual-cycle-independent differences in response to CRH stimulation compared to healthy controls. A greater response to CRH stimulation was found in women with menstrual cycle related disorders (Rubinow & Schmidt, 1995). These findings suggest that changes in non-reproductive endocrine systems can also precipitate menstrual cycle related mood disorders (Rubinow & Schmidt, 1995).

Furthermore, it has been suggested that the menstrual cycle does not only impact on mood and symptoms but also affects cognitive functioning. A lower performance of women during the mid-luteal phase compared to the menstrual phase (low oestrogen/low progesterone) has been reported, with testosterone having a positive and oestradiol having a negative effect on spatial cognition (Hausmann,

Slabbekoorn, Van Goozen, Cohen-Kettenis, & Güntürkün, 2000). Working memory function has been found to be impaired in the luteal phase in healthy controls as well as in women with premenstrual dysphoric syndrome (Man, MacMillan, Scott, & Young, 1999). It has also been reported that oestradiol levels correlate positively with verbal fluency and negatively with mental rotations during the menstrual cycle (Maki, Rich, & Shayna Rosenbaum, 2002). In a study conducted by Symonds and colleagues (2004), it was found that changes in the menstrual cycle have an effect on neurocognitive functioning in healthy female volunteers (Symonds et al., 2004). Participants were assessed during the mid-follicular (high oestrogen/low progesterone) and the late-luteal phase on mood, neurocognitive function, basal cortisol and dehydroepiandrosterone (DHEA). Data showed that compared to the mid-follicular phase, women were impaired in verbal fluency and had faster reaction times on a continuous performance task during the late-luteal phase. Also mood, cortisol and DHEA were decreased in the luteal phase. These results indicate that HPA axis function is lower in the luteal phase in healthy female volunteers compared to the follicular phase of the cycle, which may in turn influence mood and neurocognitive function (Symonds et al., 2004).

Differences in the levels of oestrogens have been associated with verbal memory impairment and differences in prefrontal functioning in previous functional magnetic resonance imaging (fMRI) studies in healthy pre-menopausal women pre-, during, and post-acute ovarian hormone suppression using Gonadotropin Hormone Releasing Hormone agonists (GnRHa) (Craig et al., 2008; Craig et al., 2007). The impairment reversed following the resolution of ovarian hormone suppression. In a recent fMRI study conducted by Thimm, Hausmann and Sturm (2013), it was found that the menstrual cycle also influenced selective attention and its underlying functional cortical networks (Thimm, Weis, Hausmann, & Sturm, 2013). Healthy female volunteers were assessed during the menstrual, follicular and the luteal phase on a go/no-go task. The performance results suggested a functional cerebral asymmetry toward the left hemisphere in selective attention during the menstrual phase, which was however not associated with changes in the imaging data. Yet, a functional connectivity analysis of the data showed a weaker negative correlation during the luteal phase between the left hemispheric frontal areas and the left inferior

parietal region and the right middle frontal gyrus, possibly reflecting a reduction of inhibition of the left medial frontal cortex on the areas (Thimm et al., 2013).

Taken together, studies conducted to assess the effects of the menstrual cycle show the importance of taking the hormonal variations associated with it into account in studies assessing patients with mood disorder or psychoses, as well as in healthy women, as biological and neurocognitive measures can be heavily influenced by these variations. In addition to hormonal variations in women at risk of or suffering from postpartum psychosis, it is also likely that changes in neurotransmitter levels play an important role. Hormones may also interact with neurotransmitters to increase the risk of developing the disorder. A neurotransmitter that has been investigated, because of its proposed involvement in psychotic disorders, is dopamine.

1.3.1.4 Dopamine

Dopamine dysfunction has been considered to alter the appraisal of stimuli, potentially resulting in the development of psychosis (Howes & Kapur, 2009). In addition, it has been proposed that oestrogens affect the neurotransmitter dopamine (Cyr et al., 2002; Gogos, Kwek, & Buuse, 2012; Howes & Kapur, 2009). Therefore, researchers have suggested that dopamine has an important role in postpartum psychosis (Cookson, 1982; Meakin, Brockington, Lynch, & Jones, 1995; Wieck et al., 1991). It is possible that the postpartum fall in oestrogens leads to an increased sensitivity to dopaminergic stimulation, which in turn triggers the onset of postpartum psychosis (Cookson, 1982; Meakin et al., 1995; Wieck et al., 1991).

Based on the assumption that oestrogens also modulate dopamine function, the response of growth hormone (GH) to the dopamine agonist apomorphine was assessed on the fourth day postpartum in women at high risk due to a history of bipolar or schizoaffective disorder. The GH response is indicative of the responsiveness of dopamine sensitive neurons in the brain (Wieck et al., 1991). Researchers showed that illness onset in eight of the 15 women was associated with an increased sensitivity, since their GH response was enhanced, compared to the other women at high risk who did not develop postpartum psychosis and 15 healthy controls (Wieck et al., 1991).

Although a promising start, these results were not confirmed by a replication study, which found no increase in sensitivity of dopamine neurons in three women who developed postpartum psychosis (Meakin et al., 1995). Another study assessing the sensitivity of dopamine neurons on the fourth day postpartum used apomorphine in a series of 25 women with bipolar or schizoaffective disorder, 15 depressed women and 15 healthy controls. They found that the women with bipolar or schizoaffective disorder had a significantly elevated GH response, with the highest response in those who developed depression (R. Kumar et al., 1997). Given the positive association found in the two studies with a larger number of participants, the current best evidence suggests that dopamine is important for the development of postpartum psychosis.

As well as the GH response, the prescription of bromocriptine, a dopamine agonist which inhibits prolactin, has been associated with postpartum psychosis (Brockington & Meakin, 1994; Canterbury, Haskins, Kahn, Saathoff, & Yazel, 1987; Iffy, Lindenthal, Szodi, & Griffin, 1989). Bromocriptine is often prescribed to stop lactation (i.e. preventing or reducing milk production). Similar to the results found in studies assessing hormones in postpartum psychosis, results from investigating dopamine changes in women with postpartum psychosis are inconsistent, with some studies showing an association (Wieck et al., 1991) while others do not (Meakin et al., 1995). This makes it difficult to draw any firm conclusions. However, based on the assumption that there are changes in hormone and neurotransmitter levels, some researchers investigated whether variations in genes associated with these hormones and neurotransmitters might be underlying these changes.

1.3.1.5 Genes

Since there has been some level of agreement over the role of oestrogen in postpartum psychosis, research has aimed to investigate whether alterations in genes known to be influenced by oestrogen levels are present in women with postpartum psychosis. Jones et al. (2000) proposed that a certain variation within the oestrogen receptor gene would be associated with susceptibility to bipolar disorder or postpartum psychosis (Jones et al., 2000). Their sample consisted of 219 bipolar women, including 26 women with a postpartum psychotic episode, and 219 controls.

They did not find that this genetic variation was associated with susceptibility to bipolar disorder or postpartum psychosis.

Oestrogens exert a wide range of actions on different neuronal systems (e.g. dopaminergic and serotonergic pathways) (Cyr et al., 2002; Gentile, 2005; Gogos et al., 2012). Therefore, serotonergic genes are plausible candidates for assessing a possible association with postpartum psychosis. However, results have been mixed. It was found that certain variations of the serotonin transporter gene were associated with vulnerability to bipolar affective postpartum psychosis (Coyle, Jones, Robertson, Lendon, & Craddock, 2000; H. B. K. Kumar et al., 2007) while others were not (Robertson et al., 2003). In addition to investigating serotonergic genes, whether there are any chromosomal alterations associated with postpartum psychosis was also investigated. In a genetic linkage genome study investigating 54 women with a first-degree relative who suffered from postpartum psychosis, a strong linkage to chromosome 16p13 and 8q24 was found, possibly defining a genetically relevant subtype of bipolar disorder (Jones & Craddock, 2007; Jones et al., 2007).

Given the link with increased cortisol levels found in postpartum psychosis, genetic variations of the glucocorticoid receptor were also investigated. The study did not find any differences between women suffering from postpartum psychosis, those suffering from psychoses unrelated to childbirth, and healthy controls (Feng et al., 2000).

In summary, studies assessing variations in serotonergic genes have found some association with postpartum psychosis and bipolar disorder. Also, a strong linkage to chromosome 16p13 and 8q24 has been observed. No association was found in genetic variations in the oestrogen or glucocorticoid receptors. In the future, more specific studies will need to clarify the precise relationship and implications of these findings.

1.3.2 Sleep loss

Another risk factor that has been discussed in the literature is sleep loss and it has been suggested as the final common pathway in the development of postpartum psychosis in susceptible women (Sharma & Mazmanian, 2003). Sleep loss is seen as a major precipitant for postpartum psychosis (Sharma et al., 2004; Sit et al., 2006).

Pregnancy and the postpartum period are associated with significant changes in sleep patterns (e.g. more awakenings and sleep disruptions), often occurring in the first night postpartum (Karacan, Williams, Hirsch, McCaulley, & Heine, 1969; Sharma & Mazmanian, 2003). In a study assessing loss of sleep as a result of length of labour and time of delivery, it was found that insomnia was the most frequent (experienced by 87%) and earliest symptom in women developing postpartum psychosis (Sharma et al., 2004). Sleep loss is also more pronounced in primipara women (i.e. women having their first child), who have been found to be at a higher risk of developing postpartum psychosis (P. Agrawal et al., 1990; V. Bergink et al., 2011; Kendell et al., 1987; Kendell, Rennie, et al., 1981; Kirpinar et al., 1999; Kisa et al., 2007; Meltzer & Kumar, 1985; Schöpf et al., 1984; Videbech & Gouliaev, 1995).

Oestrogens play a role in the regulation of the circadian cycle and the huge drop of oestrogen levels that occurs following delivery has the potential of triggering insomnia (Hunter, Rychnovsky, & Yount, 2009; Sharma & Mazmanian, 2003). Nonetheless, findings are inconsistent. In a different study, changes in sleep and wake activity were compared during pregnancy and in the postpartum period in women with a history of bipolar disorder as well as postpartum psychosis and healthy controls and no significant differences were found between groups (Bilszta et al., 2010).

Results of studies assessing the role of sleep loss in postpartum psychosis are inconsistent and further research is needed to establish its precise role, as sleep loss might in turn be associated with the amount of stress the women experience (e.g. due to difficulties during the delivery or social stressors). Moreover, sleep loss might represent an early symptom of postpartum psychosis rather than being a risk factor in itself. Contrary to other areas such as sleep loss, clinical and sociodemographic correlates have received more attention in previous research.

1.3.3 Clinical and sociodemographic correlates

The common view has been that postpartum psychosis is not typically precipitated by stressful life events (Brockington et al., 1990; R. Kumar et al., 1993; McNeil, 1988b; Paffenbarger & McCabe, 1966; Protheroe, 1969). Women with postpartum psychosis have been reported to have a similar amount or even less exposure to acute

stressful life events before symptom onset compared to women who did not develop symptoms in the postpartum period (Brockington et al., 1990; Dowlatshahi & Paykel, 1990).

However, findings are inconsistent across the literature. Some studies found that postpartum psychosis is associated with both stressful life events (e.g. caesarean section, having the first child) (P. Agrawal et al., 1990; V. Bergink et al., 2011; Kendell et al., 1987; Kendell, Rennie, et al., 1981) as well as social stressors (e.g. being single, higher maternal age, living in a poor socioeconomic environment, or having a lower educational level) (Cheetham et al., 1981; Kendell et al., 1987; Kendell, Rennie, et al., 1981; Nager et al., 2006; Nager et al., 2012; Paffenbarger, 1961; Paffenbarger & McCabe, 1966; Valdimarsdóttir, Hultman, Harlow, Cnattingius, & Sparén, 2009).

It seems plausible that given the importance of stressful life events and social stressors in triggering or exacerbating other mental disorders such as psychoses unrelated to childbirth (Aiello et al., 2012; Bennett & Maxwell, 2008; Schäfer & Fisher, 2011), both play an important role in postpartum psychosis. Although a lot of research has investigated stressful life events and social stressors in postpartum psychosis, results remain inconsistent. It will be important to determine more specifically in large epidemiological samples whether postpartum is indeed associated with stressful life events or social stressors. Other research areas that have received little attention in postpartum psychosis research are the potential cognitive, emotional, and neuroimaging correlates.

1.3.4 Cognitive, emotional and neuroimaging correlates

Given the close relationship between postpartum psychosis and bipolar disorder, as well as psychoses unrelated to childbirth, it could be expected that women with postpartum psychosis display similar cognitive, emotional or neuroimaging deficits as those found in these disorders (Bora, Yücel, & Pantelis, 2010; Bowie & Harvey, 2005; Brüne, 2005; Y. Chen, Cataldo, Norton, & Ongur, 2012; Hoertnagl et al., 2011; Kohler, Walker, Martin, Healey, & Moberg, 2010; Libby, Yonelinas, Ranganath, & Ragland, 2012; Malhi et al., 2007; Mur, Portella, Martínez-Arán, Pifarré, & Vieta, 2007; L. J. Robinson et al., 2006; Rocca, Heuvel, Caetano, & Lafer,

2009; Sachs, Steger-Wuchse, Kryspin-Exner, Gur, & Katschnig, 2004; J. B. Savitz, van der Merwe, Stein, Solms, & Ramesar, 2008; Valli, Tognin, Fusar-Poli, & Mechelli, 2012; Whittaker, Deakin, & Tomenson, 2001). Until today, these aspects have not been investigated in postpartum psychosis and only three preliminary studies have investigated cognition and potential brain changes. In one study assessing attention and working memory by using a serial subtraction and a digit span test, women with postpartum psychosis were not found to perform differently from healthy controls (Melges, 1968). Using computed tomography (CT), ventricular cerebrospinal fluid (CSF) spaces were investigated in women with postpartum psychosis and compared to women with psychoses or bipolar disorder unrelated to childbirth, as well as to healthy controls. It was found that the left ventricular area, planimetric ventricular-brain ratio and superior cerebellar cistern volume were larger in the first group than the other two (Lanczik et al., 1998). These widespread changes could indicate an unspecific structural vulnerability marker (Lanczik et al., 1998).

One fMRI case study conducted in a monozygotic pair of twins discordant for postpartum affective psychosis, investigated whether there was any differential activation in the orbitofrontal cortex (OFC; Brodmann area 47) between the two women while viewing emotional film excerpts. The study found less activation in the OFC in the woman with the history of postpartum psychosis (later diagnosed with schizoaffective disorder), indicating a disturbance in the integration of emotionally relevant information, which is a key characteristic in bipolar disorder and psychoses unrelated to childbirth (Drevets, 2007; Fahim, Stip, Mancini-Marie, Potvin, & Malaspina, 2007; van der Schot, Kahn, Ramsey, Nolen, & Vink, 2010).

Given the lack of research on these aspects, no firm conclusions can be drawn. However, cognitive and emotional dysfunction are key impairments found in both bipolar disorder and psychoses unrelated to childbirth (Bora et al., 2010; Bowie & Harvey, 2005; Brüne, 2005; Y. Chen et al., 2012; Hoertnagl et al., 2011; Kohler et al., 2010; Libby et al., 2012; Malhi et al., 2007; Mur et al., 2007; L. J. Robinson et al., 2006; Rocca et al., 2009; J. B. Savitz et al., 2008; Valli et al., 2012). Impairments in cognitive functioning including working and verbal memory have been strongly associated with bipolar disorder and psychoses unrelated to childbirth (D.M. Barch & Ceaser, 2012; Bora et al., 2010; Brewer et al., 2006; R.E. Carrión et al., 2011; I.N. Ferrier, Stanton, Kelly, & Scott, 1999; Lee & Park, 2005; Libby et al., 2012; L. J.

Robinson et al., 2006; J. B. Savitz et al., 2008; Valli et al., 2012). These impairments do not seem to qualitatively differ between diagnostic groups (i.e. schizophrenia, schizoaffective disorder, bipolar disorder and major depressive disorder), although the schizophrenia group shows the most severe impairments (Reichenberg, 2010; Reichenberg et al., 2009; Stefanopoulou et al., 2009). In line with this result is the finding that cognitive deficits are more pronounced in bipolar patients with psychotic symptoms than in non-psychotic bipolar patients (Bora et al., 2010; Levy & Weiss, 2010; J. Savitz, van der Merwe, Stein, Solms, & Ramesar, 2009). Still, the deficits in working memory and verbal memory persist - with less intensity - during euthymic phases in bipolar patients and can be found in their first-degree relatives (Arts, Jabben, Krabbendam, & van Os, 2008; I.N. Ferrier, Chowdhury, Thompson, Watson, & Young, 2004; I.N. Ferrier et al., 1999; Reichenberg, 2010; L. J. Robinson et al., 2006; Zubieta, Huguelet, O'Neil, & Giordani, 2001). This suggests that the impairments are not only by-products of the symptoms, but are rather a trait characteristic of the illnesses (I.N. Ferrier et al., 1999; J. B. Savitz et al., 2008; Zubieta et al., 2001). In addition, impairments seem to start before symptom onset as they are present in high risk individuals (Brewer et al., 2006; R.E. Carrión et al., 2011). Cognitive dysfunction found in patients at high risk or suffering from bipolar disorder or psychoses unrelated to childbirth is also reflected in abnormalities in brain activation assessed with fMRI (C. Chen, Suckling, Lennox, Ooi, & Bullmore, 2011; Fusar-Poli et al., 2012; Glahn et al., 2005; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). Especially frontal, but also temporal, parietal and subcortical areas seem to be affected in working memory tasks (C. Chen et al., 2011; Fusar-Poli et al., 2012; Glahn et al., 2005; Minzenberg et al., 2009).

Similarly, bipolar disorder and psychoses unrelated to childbirth are associated with deficits in emotional processing (Brüne, 2005; Y. Chen et al., 2012; Hoekert, Kahn, Pijnenborg, & Aleman, 2007; Hoertnagl et al., 2011; Kohler et al., 2010; Malhi et al., 2007; Rocca et al., 2009). Deficits seem to be mainly driven by an impairment in recognising and categorising facial emotion expressions (Hooker & Park, 2002; Kohler et al., 2010). The ability to recognise facial emotion expressions is of great importance and a fundamental skill for any social interaction, work functioning and independent living in order to be able to evaluate situations and respond in an appropriate manner (Hoertnagl et al., 2011; Kee, Green, Mintz, &

Brekke, 2003; Kohler et al., 2010). Impairment in recognising emotion has been found to be related to poorer social functioning in patients with psychoses unrelated to childbirth (Hooker & Park, 2002; Poole, Tobias, & Vinogradov, 2000). In line with the findings in cognitive functioning, patients with bipolar disorder and psychoses unrelated to childbirth do not show qualitative differences in facial emotion processing and share specific aspects of facial emotion processing deficits, such as mislabelling fear (Goghari & Sponheim, 2012). Patients with psychoses unrelated to childbirth and patients with more severe psychotic symptoms have been found to show a stronger impairment in recognising emotions than patients with bipolar disorder without psychotic symptoms (Aleman & Kahn, 2005; Goghari & Sponheim, 2012; Poole et al., 2000; Rocca et al., 2009). Furthermore, impairment in emotion processing has also been reported in individuals at risk of psychosis, with similar performance to patients diagnosed with a first episode (Addington, Penn, Woods, Addington, & Perkins, 2008; G. P. Amminger et al., 2012; G.P. Amminger et al., 2012; L. K. Phillips & Seidman, 2008).

Deficits in emotional processing found in bipolar disorder as well as psychoses unrelated to childbirth have been accompanied by differential brain activation (i.e. increases as well as decreases) in cingulate, frontal, subcortical, temporal and parietal areas, when compared to healthy controls (Li et al., 2012; Liu et al., 2012; Malhi et al., 2007). These differences in brain activation have also been reported in people at risk of psychoses unrelated to childbirth, with activation levels intermediate to patients with psychoses unrelated to childbirth and healthy controls (Li et al., 2012).

In summary, there is consistent evidence for impairments in cognitive and emotional processing and accompanying differences in brain activation in bipolar disorder and psychoses unrelated to childbirth. Given the vital role of these processes in social interactions, work life and independent functioning, it is of great importance to investigate whether women at risk of or suffering from postpartum psychosis show similar impairments with accompanying differences in brain activation.

1.3.5 Summary of research findings in postpartum psychosis

Most research on postpartum psychosis has focused on clinical and sociodemographic correlates, including clinical presentation, prognosis, and

treatment. There are many studies which have assessed women's clinical profile and background with a particular emphasis on stressful life events and social stressors. Most other results, such as those on hormonal, neurotransmitter and genetic influences and sleep in postpartum psychosis, are sparse and inconsistent. In addition, many studies suffer from important limitations such as small sample sizes or the lack of a control group, making it difficult to derive valid conclusions at this stage. However, the evidence collected so far suggests that genetic variations and hormones have an important role in postpartum psychosis, possibly affecting neurotransmitters and sleep. It will be important in the future to target these areas in order to investigate potential triggers and correlates of postpartum psychosis.

Other important areas have been almost completely neglected in postpartum psychosis research. These include cognitive, emotional, and neuroimaging markers. This is surprising, given that cognitive and emotional dysfunctions are considered key impairments in bipolar disorder and psychoses unrelated to childbirth. As a diagnosis of these disorders puts women at high risk of developing postpartum psychosis, it is of great significance to assess whether these processes are also impaired in women at risk of or suffering from postpartum psychosis.

1.4 Rationale

Despite its rare occurrence, postpartum psychosis is a severe disabling illness which is extremely important to investigate. There must be a focus on the possibility of preventing it and the potential of therefore preventing serious consequences for mother and child. Most studies investigating postpartum psychosis have focused on clinical presentation, prognosis, and treatment. Important questions about the potential cognitive, emotional, and neuroimaging correlates that are considered key impairments in bipolar disorder and psychoses unrelated to childbirth have not been addressed. Investigating whether there are potential verbal, working or facial emotion processing deficits in women with postpartum psychosis is essential in order to shed light on the pathophysiology of this disorder and to increase the knowledge and understanding of cognitive and emotional functioning in postpartum psychosis. Knowledge about these processes could potentially help in predicting future onset of postpartum psychosis and could also assist with treatment and recovery and a

profound understanding may help clinicians in developing individual management strategies and implementing targeted cognitive trainings or interventions.

Therefore, in the present study, the aim is to investigate for the first time whether women at risk of postpartum psychosis have cognitive, emotional, or neuroimaging impairments within one year postpartum that are typically associated with bipolar disorder and psychosis unrelated to childbirth. Women were included in the study when they were at risk of postpartum psychosis due to a history of bipolar or schizoaffective disorder, a previous diagnosis of postpartum psychosis according to the DSM-IV, or if they had a first-degree family history of postpartum psychosis. To keep the sample homogenous, we did not include women with other psychoses unrelated to childbirth.

As discussed in the section 1.2 Relation to other mental disorders, having a diagnosis of bipolar disorder puts women at the highest risk of developing an episode of postpartum psychosis. Therefore, we define our high risk group as including women with this diagnosis. It is well known that patients with bipolar disorder show impairments in verbal memory and working memory as well as facial emotion processing (for an overview see paragraph 1.3.4 Cognitive, emotional and neuroimaging correlates). However, our “at risk” group as a whole includes both women with and without a history of bipolar disorder, and therefore it is important to establish if, since postpartum psychosis episodes are considered part of an affective disorder spectrum, all women considered at risk show impairments similar to those seen in bipolar disorder, independently of whether they have such a diagnosis or not. This would allow us to establish whether there is a set of neurobehavioural alterations that is common to this population of “at risk” women. In addition, it will further advance knowledge on the bipolar disorder literature, since there has been no neuroimaging study that has, thus far, investigated women with a diagnosis of bipolar disorder in the postpartum period. This approach creates the context for the novel research question: whether women who do develop postpartum psychosis differ from women who, although at risk, do not develop postpartum psychosis. Furthermore, it will provide knowledge of the cognitive, emotional and neuroimaging correlates of these postpartum episodes as this may help, if validated, the identification of a set of predictors for the development of a postpartum episode among women at risk.

The two overarching research questions were: 1) whether working memory and verbal memory as well as emotional face processing – usually impaired in people with bipolar disorder or other psychoses unrelated to childbirth - are impaired in women at risk of postpartum psychosis and 2) whether women who have had postpartum episodes show a more pronounced impairment than women who have had non-postpartum episodes only.

1.5 Hypotheses

More detailed background on the literature on working memory, verbal memory and facial processing as well as the tasks will be presented in the individual chapter introduction.

Primary hypotheses:

1. Women at risk of postpartum psychosis will show, in comparison to healthy controls, decreased brain activation in the dorsolateral prefrontal cortex during a working memory task.
2. Women at risk of postpartum psychosis will show, in comparison to healthy controls, higher brain activation of the amygdala during a facial emotion processing task.

In addition, I will test a set of exploratory, secondary hypotheses:

1. Women at risk of postpartum psychosis will show, in comparison to healthy controls, differential brain activation during a working memory and facial emotion processing task as assessed with whole brain analysis.
2. Women at risk of postpartum psychosis will show, in comparison to healthy controls, impaired working memory performance.
3. Women at risk of postpartum psychosis will show, in comparison to healthy controls, impaired verbal memory performance.
4. Impairments in verbal and working memory and differences in brain activation in working memory as well as in facial emotion processing will be more pronounced in women who had developed postpartum psychosis episodes, compared to women who had not developed postpartum psychotic episodes, and to healthy controls.

1.6 Outline

In this thesis clinical, cognitive, emotional, and neuroimaging measures of women at risk of postpartum psychosis are investigated and described. In chapter 2, the methods used in the current study will be outlined. In chapter 3, the clinical and sociodemographic correlates of the sample, including the psychiatric diagnoses, sociodemographic information, medical and obstetric history, and history of substance use as well as clinical scales, are explored and compared to previous studies on postpartum psychosis. Chapter 4 – verbal memory - will describe the assessment and findings of the performance in two verbal memory tasks. In chapter 5, the behavioural performance as well as the neuroimaging correlates of working memory will be presented. In chapter 6, neuroimaging correlates of facial emotion processing will be investigated. A specific introduction of previous literature and discussion of the results is given in each chapter. A general discussion of the findings and their implications will be given in chapter 7, together with a future outlook.

2. Chapter: Methods

In this chapter the methods used in the study will be discussed. A description of participants will be given, including recruitment procedures, inclusion criteria and reasons for exclusion. The study design as well as clinical and cognitive assessments will be presented. This will be followed by a detailed description of the neuroimaging technique used in this study, comprising the background of fMRI, and tasks and the image acquisition used. Then, the analysis methods will be outlined for the behavioural and neuroimaging data. Finally, the study procedure will be explained, covering both study visits and a statement on the personal contribution will be made.

2.1 Participants

A total of 51 women were recruited for the study according to the following inclusion criteria: women in the “at risk” group had a diagnosis of current or previous personal history of bipolar disorder, schizoaffective disorder, or postpartum psychosis and/or a family history of postpartum psychosis (N=27) (Jones & Craddock, 2001; Robertson et al., 2005). Healthy female controls had no current psychiatric disorder, no personal history of any of the above diagnoses, no family history of postpartum psychosis and did not take any medication (except nutritional supplements) at the time of recruitment (N=24). Healthy controls were matched to the “at risk” group according to IQ, ethnicity, education and the number of weeks after delivery.

Inclusion criteria for both groups were:

- 1) Pregnant or within the first year after delivery.
- 2) Age 18-45 years inclusive.
- 3) Able to communicate in English.
- 4) No fMRI contraindications (e.g. metallic implants, claustrophobia).
- 5) No severe obstetric complications.
- 6) No chronic medical condition (e.g. pulmonary, cardiac, autoimmune, or endocrine).

The study was approved by the Joint South London and Maudsley/Institute of Psychiatry Research Ethics Committee (10/H0807/14). Women at risk of postpartum psychosis were recruited through the perinatal psychiatry services of the South London and Maudsley and the Central and North West London National Health Service (NHS) Foundation Trusts. The perinatal services of the South London and Maudsley NHS Foundation Trust included the liaison perinatal psychiatry services based at King's College Hospital, St Thomas Hospital, and Croydon University Hospital and the in-patient Mother and Baby Unit at the Bethlem Royal Hospital. The Central and North West London NHS Foundation Trust included the Coombe Wood Perinatal in-patient Mother and Baby Unit at the Park Royal Centre for Mental Health.

In the UK, women are routinely screened by midwives at their first antenatal appointment and are referred to perinatal services, if they may be at risk of or are experiencing mental health problems. Only women who agreed to be contacted by a member of the healthcare team in the perinatal services were approached (for the recruitment process see Figure 2.1A and Figure 2.2). Healthy female controls were recruited via the obstetric services at King's College Hospital (for the recruitment process see Figure 2.1B). Eligible women were approached after being identified by a member of the healthcare team as being 32 weeks pregnant or over. An initial screening procedure close to the expected date of delivery took place on the phone. The number of women "at risk" and healthy controls that were not suitable (including the reasons of exclusion) is shown in Table 2.1 and 2.2. In total, three women withdrew from the study. Women gave written consent (see Appendix D) and were reimbursed for time and inconvenience.

Figure 2.1 Recruitment process I

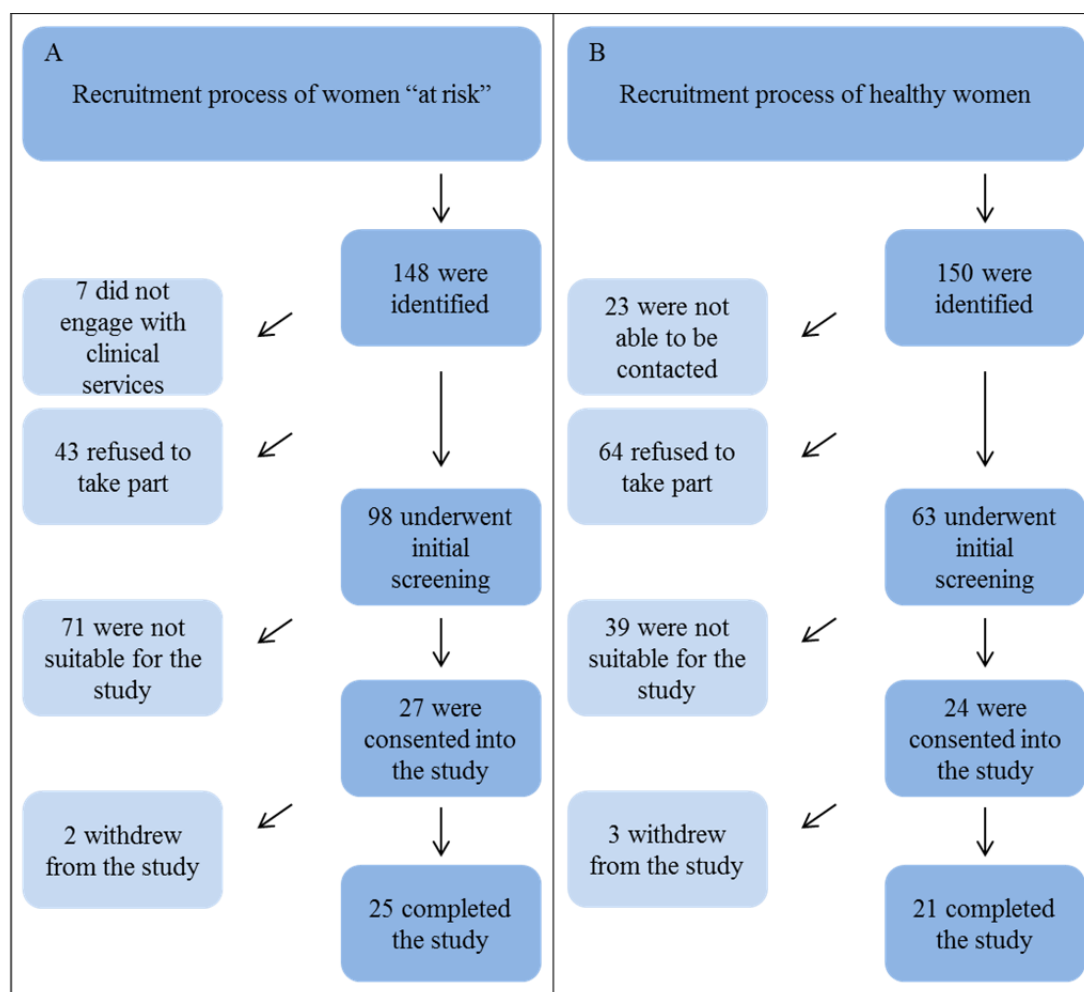


Figure 2.1 shows the recruitment process of women "at risk" (column A) and healthy controls (column B).

Figure 2.2 Recruitment process II

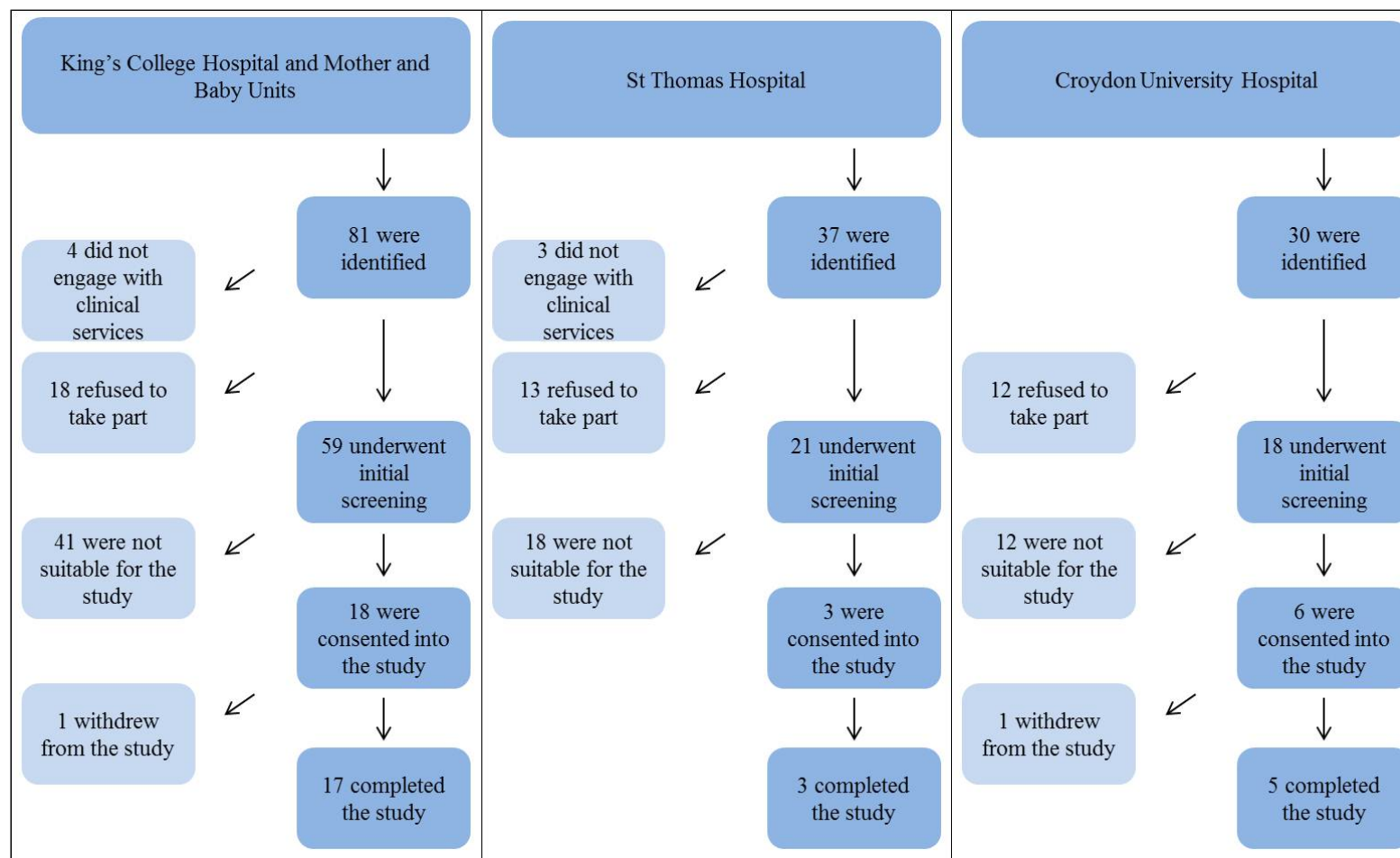


Figure 2.2 shows the recruitment process of women “at risk” for the five recruitment sites (King’s College Hospital and the two Mother and Baby Units (first column) St Thomas Hospital (second column) and Croydon University Hospital (third column)).

Table 2.1 Reasons for exclusion of women “at risk”

N=20	Follow-up diagnosis of schizophrenia/psychosis unrelated to childbirth
N=16	Follow-up diagnosis of major depressive disorder
N=6	Remained too unwell to be approached (within one year after delivery)
N=4	Medical condition
N=3	Baby was taken into foster care
N=3	Pregnancy did not result in a live birth and it was considered too stressful to take part
N=2	Not fluent in English
N=2	Termination of pregnancy
N=1	Learning difficulties (IQ < 80)
N=1	MRI contraindications
N=13	Other (e.g. not taken under the care of the perinatal psychiatry team)
N=71	Total of excluded women

Table 2.2 Reasons for exclusion of healthy controls

N=9	MRI contraindications
N=8	Current or past psychiatric diagnoses
N=7	Not fluent in English
N=1	Medical condition
N=14	Other (e.g. did not give birth at King’s College Hospital)
N=39	Total of excluded women

2.2 Design

This study consisted of two visits using a case-control design comprising two groups (women “at risk” versus healthy controls). Both assessments took place within the first year of delivery and were separated by no more than four months from each other.

2.3 Clinical and cognitive assessments

All women underwent a general assessment consisting of the evaluation of sociodemographic information, medical and obstetric history, smoking history, tea, coffee and alcohol consumption, and information on breastfeeding. All medication taken at the time of the MRI scan was recorded. This was followed by the Structured Clinical Interview for DSM-IV Axis I Disorders (Clinician Version) (SCID-I CV) (First, Spitzer, Gibbon, & Williams, 1996). Medical records and clinical notes were also reviewed. All assessments were carried out by a trained researcher (A. Pauls), except for the logical memory I and II.

For further clinical and cognitive evaluation participants completed the following scales and assessments (these were both interview-based and self-report; see Appendix A):

2.3.1 Clinical assessments

2.3.1.1 Life event scales and family history

- 1) Brief Life Events (BLE) scale; a scale containing 12 questions investigating stressful life events over the past six months (Brugha & Cragg, 1990).
- 2) Intrusive Life Events (ILE) scale; a 10 item self-report questionnaire in which participants had to indicate whether they have *ever* suffered from stressful/intrusive life events and they had to specify the year in which these events took place (Bebbington et al., 2004).
- 3) Childhood Experience of Care and Abuse Questionnaire (CECA.Q); a questionnaire in order to assess adverse childhood experiences until the age of 17 years (Bifulco, Bernazzani, Moran, & Jacobs, 2005).
- 4) Family Interview for Genetic Studies (FIGS); an interview used to investigate diagnostic information about the relatives of participants (Maxwell, 1992).

2.3.1.2 Assessment of functioning

- 5) Global Assessment of Functioning (GAF); an assessment of the current overall (i.e. psychological, social and occupational) functioning of participants on a continuous scale; it is divided into 10 ranges of functioning (American Psychiatric Association, 1994).
- 6) Clinical Global Impressions (CGI); a scale consisting of eight items, rating the current severity of the illness of the participants (Guy, 1976).

2.3.1.3 Mood and symptom scales

- 7) Hamilton Depression Rating Scale (HAM-D); a scale consisting of 17 items assessing depressive symptoms of participants over the past two weeks (M. Hamilton, 1960).

- 8) Beck Depression Inventory (BDI); a 21 item self-report questionnaire investigating the intensity of depression over the past few days (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961).
- 9) Young Mania Rating Scale (YMRS); a scale containing 11 items assessing the severity of manic symptoms over the past 48 hours (Young, Biggs, Ziegler, & Meyer, 1978) .
- 10) Positive and Negative Syndrome Scale (PANSS); a scale consisting of 30 items measuring the prevalence of positive and negative psychotic symptoms over the last seven days (Kay, Fiszbein, & Opler, 1987).

2.3.1.4 Stress, anxiety and sleep scales

- 11) State-Trait Anxiety Inventory (STAI); a 40 item self-report questionnaire assessing anxiety in the specific situation and as a general trait (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983).
- 12) Perceived Stress Scale (PSS); a 11 item self-report questionnaire assessing the degree to which events during the last month have been perceived as stressful (S. Cohen, Kamarck, & Mermelstein, 1983).
- 13) Athens Insomnia Scale (AIS); a self-report questionnaire quantifying sleep difficulty over the past two weeks based on the ICD-10 criteria, which consist of eight items (Soldatos, Dikeos, & Paparrigopoulos, 2000).

2.3.2 Cognitive assessments

- 1) Wechsler Test of Adult Reading (WTAR); a test in which participants have to read 50 English words with irregular pronunciations aloud, was used in order to estimate premorbid intellectual functioning (Wechsler, 2001).
- 2) Verbal memory assessments. Participants completed the logical memory test I and II, part of the Wechsler Memory Scale (WMS-III), in order to assess auditory-linguistic immediate and delayed memory (Abikoff et al., 1987; Wechsler, 1997). Participants also completed a remember-know paradigm (Tulving, 1985), administered on a laptop using E-prime (W. Schneider, A. Eschman, & A. Zuccolotto, 2002; W. Schneider, A. Eschman, & A. Zuccolotto,

2002). Further descriptions of the assessments can be found in chapter 4 – verbal memory.

The WTAR and the logical memory were recorded on an Olympus WS-450S Digital Voice Recorder and rated by a trained native English speaking researcher.

2.4 Neuroimaging

All women underwent an MRI scan at the Centre for Neuroimaging Sciences, at King's College London, in order to assess brain function and structure. The following section will give a short overview of the background of MR imaging, the image acquisition and parameters for the tasks used in the current study.

2.4.1 Background of fMRI

In this section, the physics underlying MR imaging will be introduced, followed by a brief description of the principles of functional MRI and an outline of the task designs used in the current study.

2.4.1.1 Nuclear Spins

Hydrogen nuclei are most commonly imaged using MRI (Brown, Perthen, Liu, & Buxton, 2007; Huettel, Song, & McCarthy, 2004). They consist of single protons spinning around their own axis (Huettel et al., 2004). This spinning (referred to as spin angular momentum) generates an electrical current due to the positive charge of the proton, which in turn produces a small magnetic dipole and torque when placed in a magnetic field. In the absence of a magnetic field, spins are distributed randomly because of thermal effects, and the sum of all magnetic moments from the spins in different orientations (i.e. the net magnetisation) is very small (Brown et al., 2007; Huettel et al., 2004). In order to align the spins and increase net magnetisation, they have to be placed in an external magnetic field (Huettel et al., 2004); (see Figure 2.3).

Figure 2.3 The random spin orientations of protons

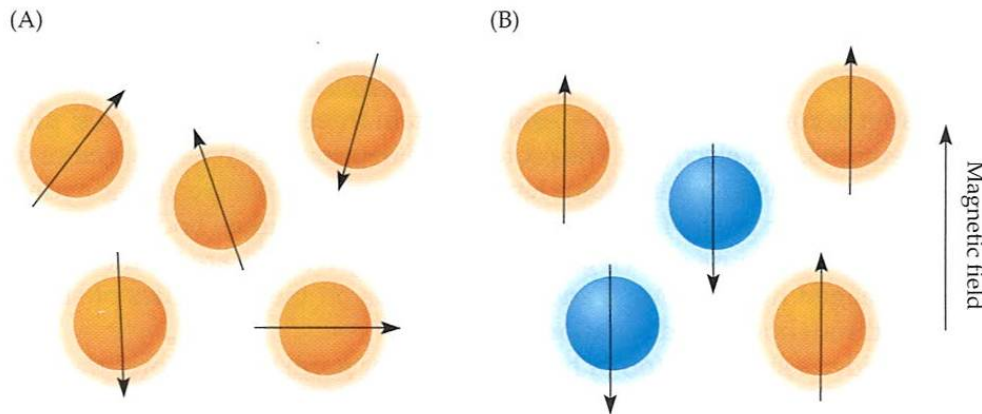


Figure 2.3 (taken from Huettel et al., 2004) shows protons having random spin orientations in the absence of a magnetic field (A) and protons aligned either parallel to or antiparallel to the main axis after being placed into a magnetic field (B) (Huettel et al., 2004).

2.4.1.2 Spins in an external magnetic field

In an external magnetic field, spins can be parallel to the magnetic field (i.e. in a low energy state) or antiparallel to the magnetic field (i.e. in a high energy state) (Huettel et al., 2004) (Figure 2.4). At equilibrium, there are more spins in the low energy state which creates a weak net magnetisation (Brown et al., 2007), the size of which is determined by the temperature and strength of magnetic field (Brown et al., 2007). To excite a spin from the lower to the higher energy state requires an electromagnetic wave at the Larmor frequency. This is the same frequency at which the spin precesses around the main magnetic field.

2.4.1.3 Net magnetisation of a spin system

The net magnetisation can be divided into two components: longitudinal (parallel to the external magnetic field) and transverse (perpendicular to the external magnetic field) (Huettel et al., 2004). The transverse components will cancel each other out, so that the net magnetisation is oriented along the longitudinal. The net magnetisation forms the basis of the magnetic resonance signal (see Figure 2.5).

Figure 2.4 Protons in antiparallel and parallel states

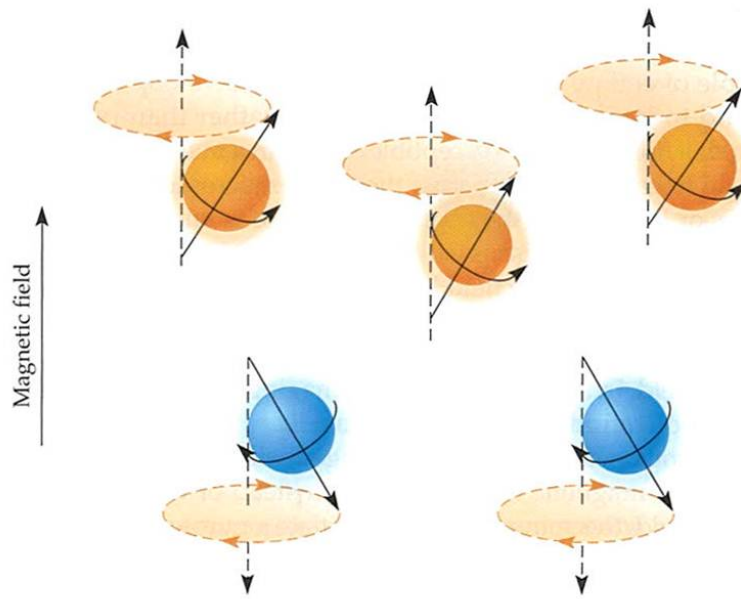


Figure 2.4 (taken from Huettel et al., 2004) shows protons in antiparallel/high energy (shown in blue) and parallel / low energy (shown in orange) states (Huettel et al., 2004).

Figure 2.5 The net magnetisation

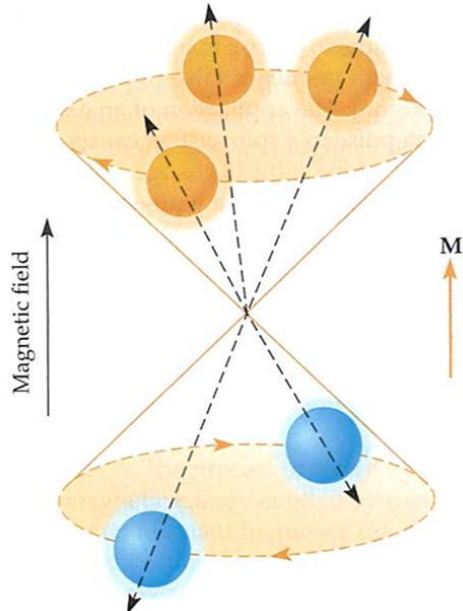


Figure 2.5 (taken from Huettel et al., 2004) shows the net magnetisation, which is determined by the difference between the number of spins in parallel and antiparallel states (Huettel et al., 2004).

2.4.1.4 Excitation and reception

By applying a radiofrequency pulse at the frequency matching the precession, spins can be tipped by a certain angle called a “flip angle” (Brown et al., 2007). Spins can be tipped into the transverse plane by a 90-degree excitation pulse. When the pulse is turned off again, the protons return to their low energy state while emitting energy equal to the difference between the two states (at the Larmor frequency). The resulting magnetic resonance signal can be measured by a receiver coil (i.e. a process known as reception; see Figure 2.6) (Huettel et al., 2004).

Figure 2.6 Changes between states due to absorption or release of energy

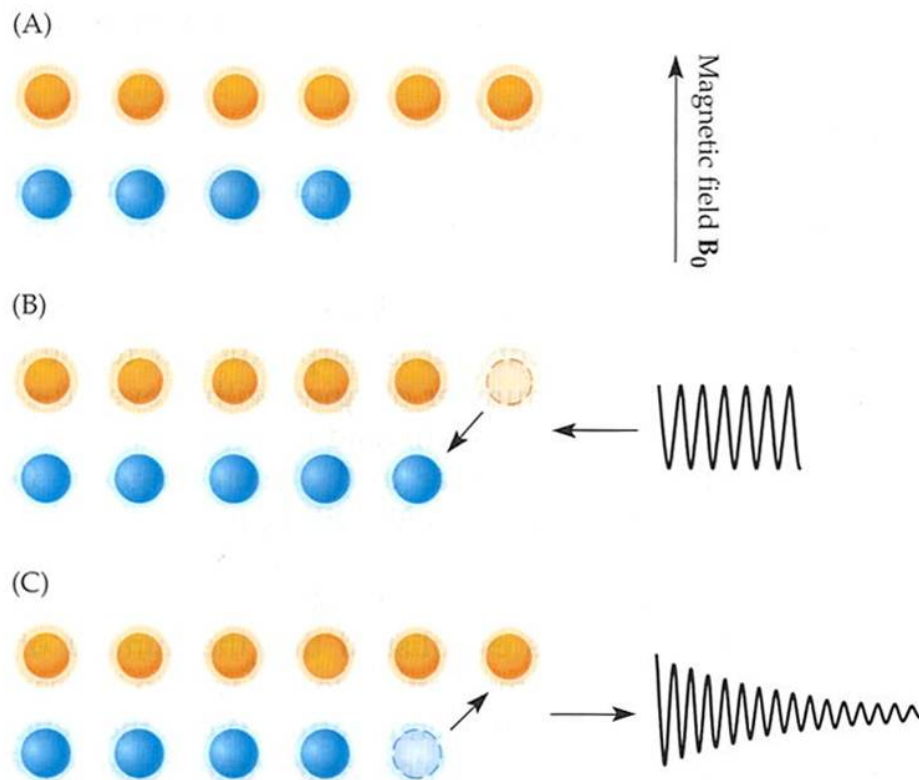


Figure 2.6 (taken from Huettel et al., 2004) shows the changes between states due to absorption or release of energy. (A) Spins in an external magnetic field, and more spins are in parallel (shown in orange) than antiparallel (shown in blue) states. In (B) due to a radiofrequency pulse (shown in black) spins will change from a parallel to an antiparallel state. In (C) after the radiofrequency pulse stops, spins will return to their normal state, emitting the absorbed energy (shown in black) (Huettel et al., 2004).

2.4.1.5 Relaxation

There are three relaxation mechanisms by which the spin system recovers its equilibrium (Matthews & Jezzard, 2004). The first is longitudinal recovery in which

the magnetisation of the z direction returns to equilibrium. This is a relatively slow process and is described by the time constant T_1 . The second is transverse relaxation and is described by the time constant T_2 (Huettel et al., 2004), which happens because the coherence of precessing spins reduces over time in the external magnetic field due to spin-spin interactions. Some spins precess at a higher and some at a lower frequency and so they get out of phase. Spatial inhomogeneities add to these differences in precession frequency which increases the rate of transverse decay and that effect is additive to T_2 decay (Brown et al., 2007). The combination of spin-spin interactions and magnetic field inhomogeneities are described by the time constant T_2^* (Huettel et al., 2004).

T_2^* relaxation forms the basis of the Blood Oxygen Level Dependent (BOLD) contrast in fMRI as T_2^* -weighted images are sensitive to the amount of deoxygenated haemoglobin present, which changes according to metabolic demands of active neurons (Huettel et al., 2004; Logothetis, 2003; Ogawa, Lee, Kay, & Tank, 1990). Although longitudinal and transverse relaxation take place simultaneously, they have different time constants and vary according to the tissue composition (Amaro & Barker, 2006; Huettel et al., 2004) (see Figure 2.7). Depending on the imaging parameters, different tissues (e.g. gray or white matter) have different signal intensities. An image is T_1 weighted if the relative signal intensity of voxels depends on the T_1 values of the tissue. An image is T_2 weighted when the amount of signal loss depends on the echo time.

Figure 2.7 T_1 and the T_2 decay

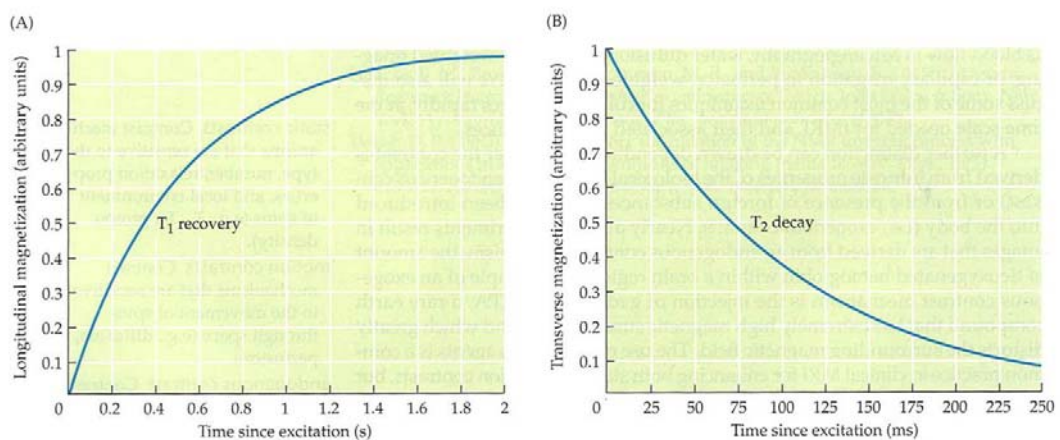


Figure 2.7 (taken from Huettel et al., 2004) shows the T_1 or longitudinal recovery and the T_2 or transverse decay of the net magnetisation (Huettel et al., 2004).

2.4.1.6 Image formation

Introducing spatial gradient magnetic fields along the x, y, and z directions varies the strength of magnetic field systematically over space and causes spins to precess at different rates in different spatial locations (Brown et al., 2007; Huettel et al., 2004). A sequence of gradient field changes is applied in order to create MR images (see Figure 2.8). An electromagnetic pulse with a range of precession frequencies excites spins within only one slice. This is followed by two spatial gradients that provide more information about the distribution of nuclei within the slice (Huettel et al., 2004). The first is frequency encoding, a gradient applied during data acquisition so that spin precession frequencies change over space; the second is phase encoding, a gradient applied before the data acquisition period so that spins can accumulate differential phase offsets over space (Huettel et al., 2004).

Often used in fMRI is echo-planar imaging (EPI), which is very rapid as the data from a complete slice are acquired after a single radiofrequency pulse. The returning MR signal is a combination of frequencies, each corresponding to a signal from a particular location (Brown et al., 2007). There are two important aspects that determine the time at which MR images are collected. The first is the time interval between successive excitation pulses (i.e. repetition time) and the second is “echo time”, the time interval between excitation and data acquisition (Huettel et al., 2004).

Figure 2.8 Spatial distributions of the x-, y-, and z-gradient magnetic fields acquisition

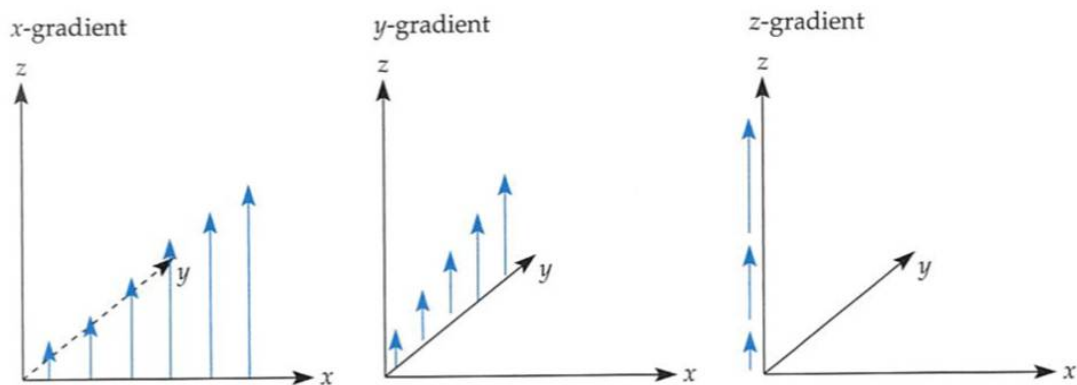


Figure 2.8 (taken from Huettel et al., 2004) shows a schematic illustration of the spatial distributions of the x-, y-, and z-gradient magnetic fields acquisition (Huettel et al., 2004).

2.4.1.7 *BOLD imaging*

The assumption behind using the BOLD contrast in fMRI is that the information processing activity of neurons increases their metabolic requirements and that the vascular system provides energy to meet these needs in the form of glucose and oxygen (bound to haemoglobin molecules) (Huettel et al., 2004). Under normal circumstances oxygenated haemoglobin is converted to deoxygenated haemoglobin at a constant rate within the capillary beds.

However, when neurons become active, the vascular system supplies more oxygenated haemoglobin than is needed by neurons. This is achieved through an overcompensatory increase in blood flow by changing both the volume of blood vessels and the velocity with which blood moves through those vessels (Huettel et al., 2004). This results in a decrease in the amount of paramagnetic deoxygenated haemoglobin (Ogawa et al., 1990). This reduces distortions of the surrounding magnetic field and therefore increases $T2^*$. Consequently, MR pulse sequences sensitive to $T2^*$ should show more MR signal when blood is highly oxygenated, as seen in Figure 2.9 (Amaro & Barker, 2006; Brown et al., 2007). The BOLD contrast appears to directly reflect neuronal activity evoked by a stimulus (Logothetis, 2002, 2003).

Figure 2.9 The BOLD signal generation.

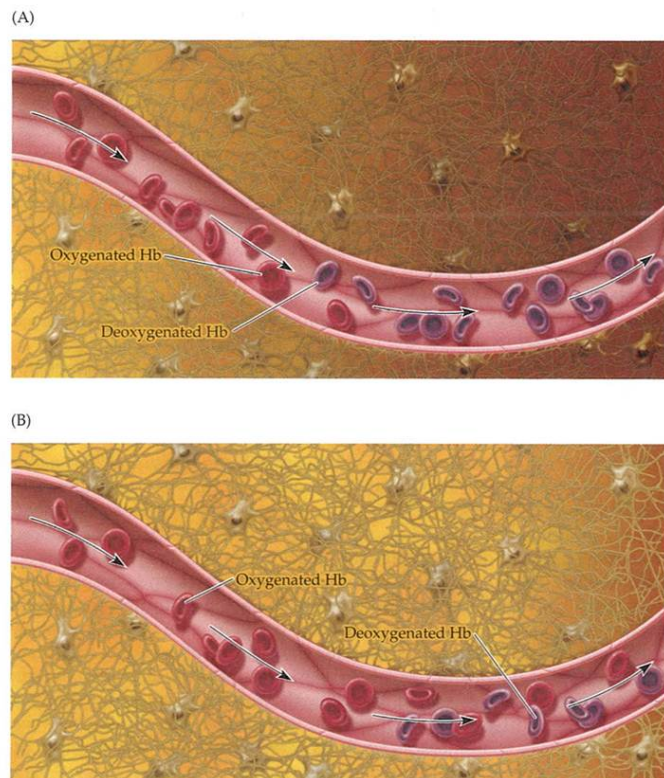


Figure 2.9 (taken from Huettel et al., 2004) shows the BOLD signal generation. Oxygenated hemoglobin is converted to deoxygenated hemoglobin at a constant rate within the capillary beds (A). When neurons become active, the vascular system supplies more oxygenated hemoglobin than necessary, resulting in a decrease in the amount of deoxygenated hemoglobin (B) and a corresponding decrease in signal loss due to T2* effects. This leads to a brighter MR image (Huettel et al., 2004).

The recorded MR signal triggered by this neuronal activity is known as the hemodynamic response (HDR), which occurs after the neuronal events that initiate it (Huettel et al., 2004). The exact form of the HDR can vary in width and length (see Figure 2.10) depending on stimuli amplitude and intensity. Sometimes the HDR starts with an initial dip (1-2 seconds) following a short stimulus, then shows a transient increase with a peak around 4-6 seconds and ends with a post-stimulus undershoot (i.e. a decrease in MR signal amplitude below baseline due to a combination of reduced blood flow and increased blood volume) (Huettel et al., 2004).

Figure 2.10 The BOLD hemodynamic response

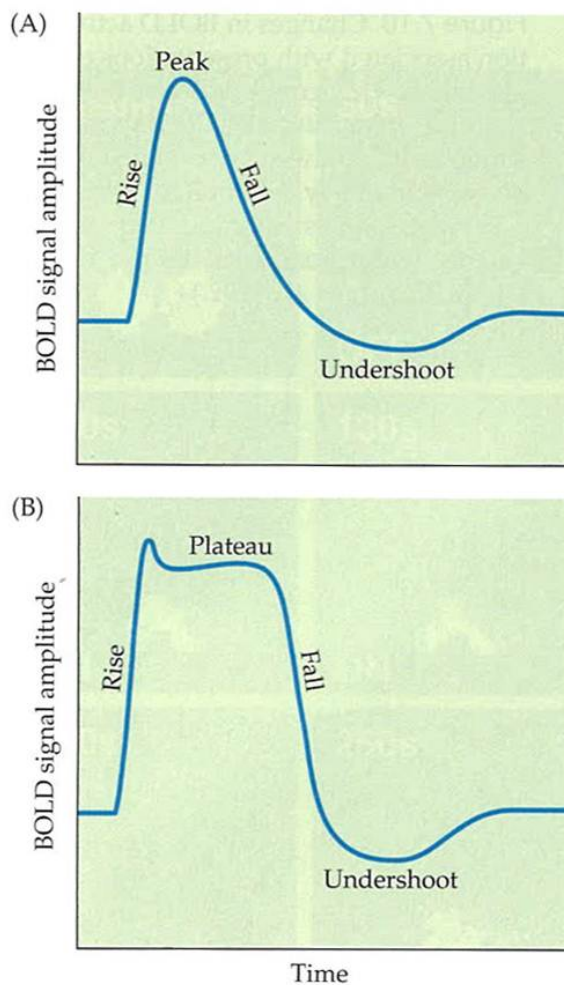


Figure 2.10 (taken from Huettel et al., 2004) shows a schematic representation of the BOLD hemodynamic response. Panel A shows the hemodynamic response to a short stimulus. Panel B shows the hemodynamic response to a block of sequential events (Huettel et al., 2004).

2.4.1.8 Designs

In this study, two types of design were used: block and event-related. For the block design (N-back paradigm) the experimental and control conditions were presented in distinct periods, each for an extended time (seconds) or block. Control blocks (with no task requirements) were used to compare each condition. In the majority of cases, block designs are superior to other designs in the efficient detection of voxels with significant activation and can identify a wide range of task related changes regardless of any variations in the timing and shape of BOLD signal (Brown et al., 2007). Furthermore, certain tasks such as memory paradigms or tasks in which the level of difficulty is varied between conditions may require a block design.

The second type of design was an event-related design (Ekman faces paradigm) in which stimuli were presented as discrete, short-duration events - separated by an interstimulus interval - and where timing and order was randomised. The assumption behind event-related designs is that neural activity will occur for short and discrete intervals. High temporal resolution is important for event-related fMRI because transient changes in the brain are associated with discrete stimuli. Provided that events of interest are presented in a random order, short interstimulus intervals can be used. Estimations of the shape and timing of the HDR are better in event-related than in block designs, but their detection power is lower (Brown et al., 2007; Huettel et al., 2004).

2.4.1.9 Tasks

The N-back task was used in order to assess working memory (Gevins & Cutillo, 1993; Kirchner, 1958; Owen, McMillan, Laird, & Bullmore, 2005). The Ekman faces paradigm was used in order to assess facial emotion processing (Ekman & Friesen, 1976; M. L. Phillips et al., 1997). For further details of the tasks see chapter 5 which is on working memory and chapter 6 which is on facial emotion processing.

2.4.2 Image acquisition

MRI data were obtained using a 3T GE Signa HDx System (General Electric, Milwaukee, Wisconsin) with an eight-channel head coil. Stimulus images were projected onto a screen, clearly visible through a periscopic mirror placed in front of participants' eyes.

2.4.2.1 High-resolution image

A high-resolution gradient-echo echo-planar image was obtained for accurate spatial normalisation, with a repetition time of three seconds and an echo time of 30ms. The flip angle was 90°. Forty three slices were acquired with a slice thickness of 3mm and a slice gap of 0.3mm. The in-plane resolution was 1.875mm².

2.4.2.2 Functional imaging

2.4.2.2.1 N-back

One hundred and eighty-six T2*-weighted images were acquired using a gradient-echo echo-planar imaging sequence. The repetition time was two seconds and the echo time was 30ms. The flip angle was 75°. Thirty nine slices were acquired interleaved from bottom to top with a slice thickness of 3.5mm and a gap of 0.5mm. The in-plane resolution was 3.75 mm² and the field of view was 24cm.

2.4.2.2.2 Ekman faces paradigm

One hundred and eighty T2*-weighted images were acquired for the Ekman faces task using a gradient echo-planar imaging sequence. The repetition time was two seconds and the echo time was 30ms. The flip angle was 75°. Thirty nine slices were acquired sequentially descending from top to bottom with a slice thickness of 3.5mm and a gap of 0.5mm. The in-plane resolution was 3.75 mm² and the field of view was 24cm.

2.5 Analysis

2.5.1 Questionnaires and performance data analysis

Questionnaires and behavioural data of the tasks were analysed using IBM SPSS 20 for Windows. All continuous data were quality checked for outliers and non-normality using the Shapiro-Wilk test. Non-parametric testing was used for all non-normally distributed data. The non-parametric Mann-Whitney U test was reported when two groups were compared. When three groups were compared, the non-parametric Kruskal-Wallis one-way analysis of variance was reported, with Mann-Whitney U tests for post-hoc pairwise comparisons carried out when a significant difference was indicated by the Kruskal-Wallis test. For repeated measures, the non-parametric Friedman's test was used (akin to a one-way repeated-measures ANOVA).

Normally distributed variables were assessed with the Analysis of Variance (ANOVA) model when three groups were compared, and with independent t-tests for two groups or as post hoc comparison when the ANOVA indicated a significant

difference between the three groups. A repeated measures ANOVA was conducted for within group comparisons (with paired t-test as follow-up when a significant difference was indicated by the repeated measures ANOVA). For post-hoc pairwise comparisons statistical significance was calculated using Bonferroni correction based on the number of pairwise comparisons. Categorical variables were assessed using the chi-square test of independence. In order to account for small numbers, Fisher's exact was calculated for the exact chi-square probability and was reported for all variables (Field, 2009). The chi-square test of independence was also reported for post-hoc pairwise comparisons of categorical variables when a significant group difference was indicated. Correlations were examined using bivariate correlation in SPSS 20.

The significant value was set at $p=.05$. However, in addition to the primary hypotheses, we also formulated exploratory secondary hypothesis for this study, concerning whole brain and performance analyses. Due to the high number of comparisons we had an increased risk of a Type I error. In order to account for multiple comparisons, an overall correction significance value was calculated based on the number of pairwise comparisons. Since there were over 50 pairwise comparisons, the overall significant value for the exploratory secondary hypothesis was set at $p=.001$. The impact of this overall significance value will be discussed separately in Chapter 7, General discussion, 7.5.3 Power and multiple comparison correction.

For more detailed information on the analyses see chapter 3 Clinical and sociodemographic correlates, chapter 4 Verbal memory, chapter 5 Working memory, and chapter 6 Facial emotion processing.

2.5.2 *Neuroimaging data analysis*

In the following section, the basic pre-processing and analysis steps of the fMRI analysis will be given. More detail can be found in the individual chapters. Beforehand, a power calculation for the two primary hypotheses will be presented along with a discussion of issues with calculating power for fMRI designs. Image pre-processing and whole-brain analysis were carried out using Statistical Parametric

Mapping software developed by the Functional Imaging Laboratory, UCL, (SPM8, www.fil.ion.ucl.ac.uk/spm/), running in Matlab 7.0.1, on a UNIX platform.

2.5.2.1 Issues with power calculations for fMRI studies

Standard statistical computations of power of detection are difficult for neuroimaging studies as the statistical inference is made from the computation of thousands of voxels per participant and following multiple comparison corrections, the parameters of which are typically calculated from the distribution of the residuals of the data after model fitting. Previous investigations indicated that BOLD related signal changes as small as 1% at the individual level are reliably detectable with groups of 10–12 participants (Brammer et al., 2004). However, up until recently, actual power calculations for fMRI designs have been lengthy and complicated and often inaccessible to non-statisticians (Mumford, 2012; Mumford & Nichols, 2008). Only lately, with the increasing demands for power calculations in neuroimaging studies, a power calculation guide has been published in order to make fMRI power calculations more accessible to all neuroimaging users (Mumford, 2012). We used these guidelines to calculate the power of the current study in detecting differences in regions of interest. According to Mumford (Mumford, 2012), if no pilot data or data from other research groups are available for a power calculation, the next option is to use results from published research. For this study it was possible to utilise previous research in bipolar disorder for the facial emotion processing task. For the working memory task previous research in schizophrenia was used as no study in patients with bipolar disorder assessing working memory with a N-back task fulfilled the minimum criteria required for power calculation according to the above mentioned guidelines (i.e. had a predefined ROI and reported the mean and the variance) (Cremaschi et al., 2013; Mumford, 2012). G*Power was used for the power calculation (Faul, Erdfelder, Lang, & Buchner, 2007).

2.5.2.2 Power calculation for the study

We calculated that an effect size of 0.72 would be needed in order to detect a statistically significant effect at an alpha of 0.05, a power of 0.80 and a sample size of 24 participants for both primary hypotheses of this study (i.e. 1) women at risk of

postpartum psychosis will show, in comparison to healthy controls, decreased brain activation in the dorsolateral prefrontal cortex during a working memory task; 2) women at risk of postpartum psychosis will show, in comparison to healthy controls, higher brain activation of the amygdala during a facial emotion processing task). In order to compare the required effect size to previous studies, we used data reported by Bleich-Cohen and colleagues (2013) for the first primary hypothesis, investigating brain activation in an N-back task in patients with schizophrenia compared to healthy controls (Bleich-Cohen et al., 2013). In line with our calculation, they found a significant difference in their predefined ROI of the dorsolateral prefrontal cortex between healthy controls (Mean = 0.45, SD = 0.31) and patients with schizophrenia (Mean = 0.24, SD = 0.21) in the two back condition with an effect size of 0.79 (see Figure 1 in Bleich-Cohen and colleagues (2013)). For the second primary hypothesis we used results of Kim and colleagues (2012). They reported a significant difference in amygdala activation between patients with bipolar disorder (Mean = 0.03, SD 0.05) and healthy controls (Mean = 0.004, SD = 0.03) during the fearful faces condition in a facial emotion paradigm with an effect size of 0.68, see Figure 3 (P. Kim et al., 2012). This suggests that our study is well powered as the required effect size is not dissimilar to that detected in previous case-control studies with neuropsychiatric patients, although as the first functional imaging study in this group we are necessarily limited in knowing the precise expected effect size. We therefore took an approach to maximise the at risk group within the constraints of the study criteria and the referral rate.

2.5.2.3 Pre-processing

Data were pre-processed in order to account for variations in timing of acquisition of slices and head movement. Data were quality checked by visually inspecting the images.

2.5.2.3.1 Slice-time correction

The data were slice-time corrected (by temporal interpolation, which is the estimation of the value of a signal at a time point that was not originally collected

using data from nearby time points (Huettel et al., 2004)) to account for inter-slice differences in BOLD signal sampling.

2.5.2.3.2 Realignment

In order to correct for participants' head movement each image in the time-series is realigned to a reference image. A two pass procedure was used whereby the images were initially realigned to the first image and then to the mean image (default procedure in SPM <http://www.fil.ion.ucl.ac.uk/spm/doc/manual/>). Six realignment parameters were applied in order to control for movement in the x-, y-, and z-axes and to control for rotation (pitch, roll and yaw).

2.5.2.3.3 Co-registration and normalisation

The high resolution gradient echo echo-planar was spatially normalised to a template image in order to get better normalisation accuracy due to improved anatomical contrast compared to the BOLD time-series images. In order to allow inter-subject comparisons, the data were spatially normalised into a standard anatomical space (Montreal Neurological Institute, MNI) (i.e. data were transformed so that they have the same image size, voxel size and shape as the template (Huettel et al., 2004)).

2.5.2.3.4 Smoothing

In order to improve statistical testing and maximise the signal-to-noise ratio and allow for inherent functional and gyral variability across participants, the resulting normalised volume time-series were spatially smoothed using a Gaussian kernel of 8mm full-width at half-maximum. A Gaussian spatial filter spreads the intensity at each voxel in the image over nearby voxels. Combining data from many subjects distributes activation across a range of voxels; using a filter that matches the expected spatial correlation of the data can increase the signal-to-noise ratio. It also implicitly reduces the effective number of multiple comparisons, as due to spatial correlation there may be many fewer maxima that exhibit significant activation (Huettel et al., 2004).

2.5.2.4 First-level analysis

Data were analysed within the framework of the general linear model. A single-subject (first-level) model was created for each session for each participant, including the following regressors of interest: 1) N-back task: correct responses to the control, and the 1-, 2-, and 3-back conditions as well as nuisance regressors (movement); 2) Ekman faces task: correct trials to neutral and fearful faces (with 50% and 100% intensity) as well as movement regressors.

2.5.2.5 Second-level analysis

Weighted linear contrasts were used to create maps of activation for each session, which were used in a group (second-level) analysis. Statistical significance was defined following voxel wise correction across the whole brain for multiple comparisons on the basis of family wise error FWE ($p < .05$). Brodmann areas (BAs) and brain regions were defined using the templates from MRIcron (www.cabiatl.com/mricro/mricron). For the specific contrasts see chapter 5 on working memory and chapter 6 on facial emotion processing.

2.5.3 Potential confounders and sources of variability

As in most studies conducted in psychiatric patient populations, there are potential confounders and sources of variability, which may affect the results and therefore need to be considered in order to be able to interpret the results correctly. The following general and more specific confounders for this particular study will be discussed in chapter 7, General discussion:

- 1) Medications
- 2) Symptoms
- 3) History of alcohol and substance abuse
- 4) Hormones and menstrual cycle effects
- 5) Time after delivery

2.6 Procedure

2.6.1 Visit 1

Following the initial screening procedure over the phone a first study visit was arranged for as soon as possible after delivery. The first visit lasted approximately two hours and took place either at participants' homes, at the Centre for Neuroimaging Sciences, Institute of Psychiatry, or, if the participant was an inpatient at a Mother and Baby Unit, at the hospital. The complete study procedure was explained to participants and they had the opportunity to read a leaflet and an information sheet and to ask detailed questions prior to providing informed consent (see Appendix D). Participants received two separate information sheets depending on whether they were in the healthy control (Information Sheet I) or "at risk" group (Information Sheet II). Participants were asked about their demographic background, medication, medical and obstetric history, smoking history, tea, coffee, and alcohol consumption, and information on breastfeeding was also collected. Subsequently, the following assessments were carried out: SCID-I CV, Intrusive Life Events Scale, Brief Life Events Scale, Childhood Experience of Care and Abuse Questionnaire, Family Interview for Genetic Studies, and the Wechsler Test of Adult Reading. At the end of the first visit an appointment for the MRI scan was arranged.

2.6.2 Visit 2

The second visit was arranged as soon as possible after the first visit (i.e. within four months) except for in the cases of seven controls who were seen at specific intervals after delivery (ranging from five to seven months) in order to match the postpartum period "weeks after delivery" to the "at risk" group. In these seven cases a short additional confirmation was carried out to ensure that no change had taken place concerning the women's mental state since the first visit. For the second visit, participants were invited to the Centre for Neuroimaging Science at the Institute of Psychiatry. Women could bring their newborn and a family member/acquaintance or, if requested, a carer was provided to look after the newborn. Prior to scanning the following clinical questionnaires were completed: Positive and Negative Syndrome Scale, Hamilton Depression Rating Scale, Young Mania Rating Scale, Beck Depression Inventory, State-Trait Anxiety Inventory, Perceived Stress Scale, Athens

Insomnia Scale, Global assessment of Functioning, and Clinical Global Impressions. Following this, women received instructions and training on the functional imaging tasks and were familiarised with the scanner environment using a “mock” scanner. Before the scanning session started, participants completed the encoding part of the verbal memory task. Scanning lasted one and a half hours, after which women completed the retrieval part of the verbal memory task and were discharged. In total, the visit lasted approximately four and a half hours. Figures 2.11 and 2.12 provide an overview of the study visits.

Figure 2.11 Overview of all study assessments

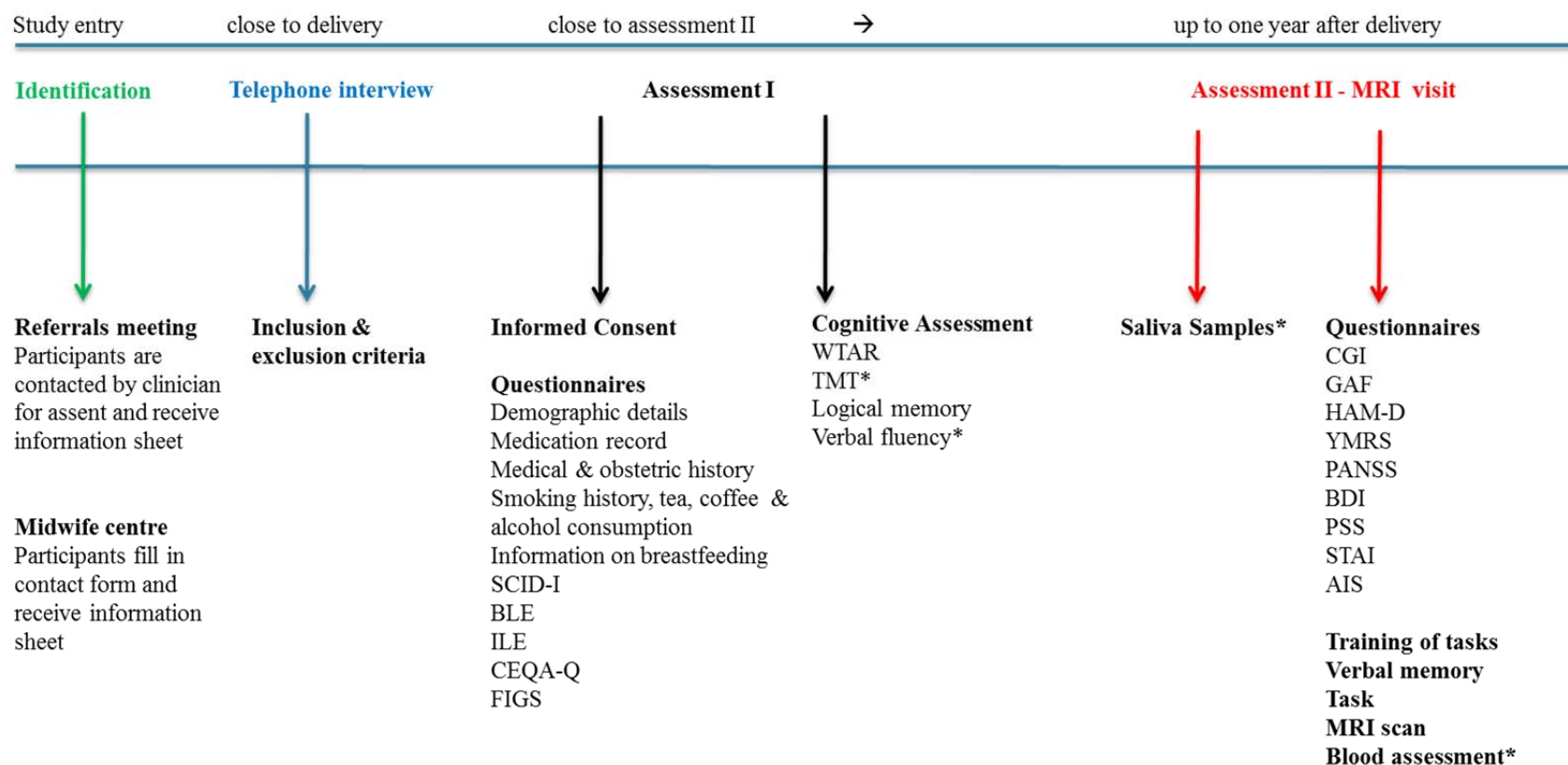


Figure 2.11 shows an overview of all study assessments. Assessments marked by an asterisk (*) are not included in this thesis. SCID-I=Structured Clinical Interview for DSM-IV Axis I Disorders; BLE=Brief Life Events; ILE=Intrusive life events; CECA.Q=Childhood Experience of Care and Abuse Questionnaire; FIGS=Family Interview for Genetic Studies (FIGS); WTAR=Wechsler Test of Adult Reading; TMT=Trail Making Test (Army Individual Test Battery, 1944; Frangou, Hadjulis, & Vourdas, 2008; Reitan & Wolfson, 1985). Verbal Fluency (Lezak, 1995; E. M. Weiss et al., 2004); CGI=Clinical Global; GAF=Global assessment of Functioning; HAM-D=Hamilton Depression Rating Scale; YMRS=Young Mania Rating Scale; PANSS=Positive and Negative Syndrome Scale; BDI=Beck Depression Inventory; PSS=Perceived Stress Scale; STAI=State-Trait Anxiety Inventory; and AIS=Athens Insomnia Scale. Blood samples were taken for hormonal assessment. Saliva samples were taken in order to assess cortisol levels.

Figure 2.12 The protocol on the MRI scanning day

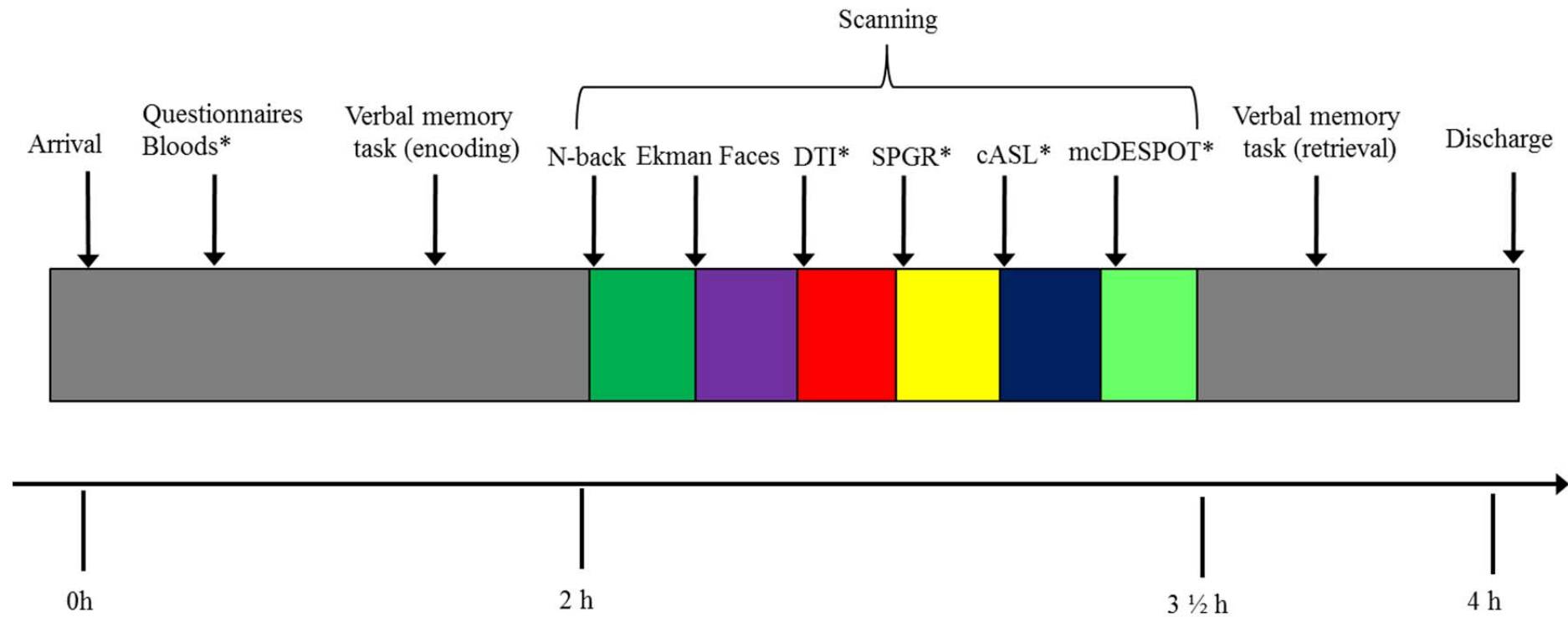


Figure 2.12 shows the protocol on the MRI scanning day. Assessments marked by an asterisk (*) are not included in this thesis. H=hours. DTI=Diffusion Tensor Imaging, an established imaging method for the assessing microstructure and architecture of the brain (including aspects of neuronal fiber coherence, axonal density etc.) based on the measure of tissue water diffusion. SPGR=coronal spoiled echo gradient sequence, an imaging sequence used in order to obtain structural images of the brain. cASL=continuous Arterial Spin Labelling, a perfusion imaging technique that measures blood flow by labelling spins with excitation pulses (Huettel et al., 2004). And mcDESPOT, a novel method that provides a voxel-by-voxel estimate of myelin content throughout the brain (S. C. Deoni, Rutt, Arun, Pierpaoli, & Jones, 2008).

2.7 Hypotheses and tasks

Primary hypotheses:

1. Women at risk of postpartum psychosis will show, in comparison to healthy controls, decreased brain activation in the dorsolateral prefrontal cortex during a working memory task. For this the N-back task will be used (chapter 5).
2. Women at risk of postpartum psychosis will show, in comparison to healthy controls, higher brain activation of the amygdala during a facial emotion processing task. In order to test this hypothesis, the Ekman faces task will be employed (chapter 6).

In addition, I will test a set of exploratory, secondary hypotheses:

1. Women at risk of postpartum psychosis will show, in comparison to healthy controls, differential brain activation during a working memory and facial emotion processing task as assessed with whole brain analysis. For this the N-back task (chapter 5) and the Ekman faces task will be employed (chapter 6).
2. Women at risk of postpartum psychosis will show, in comparison to healthy controls, impaired working memory performance. For this the N-back task will be used (chapter 5).
3. Women at risk of postpartum psychosis will show, in comparison to healthy controls, impaired verbal memory performance. In order to test this hypothesis, two verbal memory tasks will be used. A standardised verbal memory test (i.e. the logical memory I and II of the Wechsler Memory Scale-III) and the remember-know paradigm (chapter 4).
4. Impairments in verbal and working memory and differences in brain activation in working memory as well as in facial emotion processing will be more pronounced in women who had developed postpartum psychosis episodes, compared to women who had not developed postpartum psychotic episodes, and to healthy controls.

2.8 Personal contribution

Together with my supervisors, I was responsible for the writing and set up of the study protocol (i.e. developing a standardised clinical, cognitive and imaging core assessment package for study participants) and the application for ethical and R&D approval, as well as for the contact with the perinatal psychiatry and obstetric services at each involved site and the collaborations with the Mental Health Research Network (MHRN). During the first year of my PhD I was trained in clinical interviews and scales and psychometric testing. I completed a phlebotomy course at the South London and Maudsley NHS Foundation Trust. Together with other members of the team, I attended the perinatal liaisons meetings at King's College Hospital, St Thomas Hospital, and Croydon University Hospital during which new referrals were discussed, and I visited the Mother and Baby Units on a regular basis to identify potential participants.

I was responsible for the organisation and management of the study and recruited and conducted both study visits with all participants. Furthermore, under the supervision of Dr Mehta, I developed the verbal memory task, including the development of the word lists and the design. I was also responsible for data analysis and the write up. In addition, part of my role was the supervision of two placement BSc students and two medical doctors during their speciality training. I successfully applied under the supervision of Drs Dazzan and Mehta and Prof Williams for two grants centred on the hypotheses of the study: one was from the Psychiatry Research Trust (£46,000) as a young investigator and one was from the Central University Fund of the University of London (£2,110).

2.9 Original research data

For the frequency distributions of the performance and activation data of verbal memory, working memory, and facial emotion processing please see Appendix F. For information about medications please see Appendix B. For further questions concerning the original research data or about other matters related to the study please contact the principal investigator Dr Paola Dazzan, Institute of Psychiatry, SE5 8AF, London (Paola.Dazzan@kcl.ac.uk).

3. Chapter: Clinical and sociodemographic correlates

In this chapter an overview of the sociodemographic information and obstetric data that have been discussed in the postpartum psychosis literature will be presented. Then, results on the psychiatric diagnoses, sociodemographic information, medical and obstetric history, substance abuse, and the clinical scales that have been used in the current study will be presented and discussed in the context of the existing literature.

3.1 Introduction

As discussed in the main introduction of this thesis, certain clinical and sociodemographic correlates have been associated with a higher risk of developing postpartum psychosis. In the following section, sociodemographic information as well as obstetric data, which may be considered as stressful life events and long-term stressors, will be discussed.

3.1.1 *Sociodemographic information*

Postpartum psychosis affects people from all social and occupational backgrounds (M. R. Oates, 2009). However, certain disadvantageous social factors in particular have been linked to the development of postpartum psychosis. Some studies have found that being unmarried (i.e. being single) puts women at an increased risk of developing postpartum psychosis (Cheetham et al., 1981; Kendell et al., 1987; Kendell, Rennie, et al., 1981; Paffenbarger, 1961; Paffenbarger & McCabe, 1966). Not having a partner and therefore potentially lacking social support may overwhelm and subsequently increase the stress experienced by a single mother. Indeed, it has been found that problems in the social support of women, such as poor partner relationship, emotional problems during the pregnancy, or not living with the baby's father, were also associated with postpartum psychosis (Bilszta et al., 2010; Marks et al., 1992; Nager et al., 2005, 2006). There is no evidence to date that women who develop postpartum psychosis have had a particularly difficult childhood (Bratfos &

Haug, 1966; Valdimarsdóttir et al., 2009), although higher parental disapproval has been found in women who experienced this disorder (Cheetham et al., 1981).

Women with a poor socioeconomic background and who are living in a deprived area (also those living in rural areas) are at a higher risk of developing postpartum psychosis (Kirpinar et al., 1999; Nager et al., 2006). This may be because of exposure to stressors such as a higher likelihood of witnessing crime and violence and also through having less social support (Nager et al., 2006). Being an immigrant is also associated with a higher risk of developing postpartum psychosis (Kendell, Wainwright, Hailey, & Shannon, 1976; Paffenbarger, 1961), potentially because of social stressors such as inadequate housing and cultural isolation. A lower level of education, which again may be linked to having a poorer socioeconomic background or living in a poorer area, also puts women at a higher risk of developing postpartum psychosis and further non-postpartum relapses (Kirpinar et al., 1999; Nager et al., 2012). Taken together, despite disagreement in the literature, certain sociodemographic factors have been found to increase the risk of postpartum psychosis for some women. A stronger association, however, has been found with certain obstetric risk factors (Sit et al., 2006).

3.1.2 Obstetric data

Certain obstetric factors have been reported consistently in the literature as putting women at a higher risk of postpartum psychosis. One factor is that women who are having their first child are at a higher risk of developing postpartum psychosis. Percentages of primiparity found among women with postpartum psychosis are high (typically more than 60%) (P. Agrawal et al., 1990; V. Bergink et al., 2011; Blackmore et al., 2006; Cheetham et al., 1981; Kendell et al., 1987; Kendell, Rennie, et al., 1981; Kirpinar et al., 1999; Kisa et al., 2007; Meltzer & Kumar, 1985; Paffenbarger, 1961; Paffenbarger & McCabe, 1966; Protheroe, 1969; Schöpf et al., 1984; Videbech & Gouliaev, 1995). The idea that this high percentage is accounted for by the fact that women who suffered from postpartum psychosis may not have another child after an episode of this severe illness has been contradicted (Bratfos & Haug, 1966; Paffenbarger, 1961). No differences in the number of subsequent children has been found between women with postpartum psychosis and other

women (Bratfos & Haug, 1966; Paffenbarger, 1961). Although the precise mechanism is not clear, it seems likely that having a first child imposes a greater social stressor for women and potentially triggers or contributes to the development of an episode of postpartum psychosis (Blackmore et al., 2006).

Another common finding is that a caesarean section is linked to an increased risk of developing postpartum psychosis (Kendell et al., 1987; Kendell, Rennie, et al., 1981; Nager, Sundquist, Ramírez-León, & Johansson, 2008; Robertson Blackmore et al., 2006). There is support for the idea that a caesarean section contributes to the development of postpartum psychosis due to being a stressful life event. It was reported that only emergency caesarean sections, indicating problems with the delivery, were associated with the development of postpartum psychosis when compared to planned caesarean sections (Nager et al., 2008).

Other complications during pregnancy or delivery, such as pregnancies that do not result in a live birth, have not been typically connected to a higher risk of postpartum psychosis, although this again has been disputed by some studies (V. Bergink et al., 2011; Blackmore et al., 2006; Kendell et al., 1987; Kendell, Rennie, et al., 1981; Kendell et al., 1976; Paffenbarger, 1961; Rehman, St Clair, & Platz, 1990; Valdimarsdóttir et al., 2009; Videbech & Gouliaev, 1995). The development of postpartum psychosis has been associated with a lower birth weight of the babies in some studies (Brockington, 1996; Paffenbarger, 1961; Paffenbarger & McCabe, 1966), although another study observed a higher birth weight (Valdimarsdóttir et al., 2009). Additionally, a shorter gestation length and preterm delivery have been found in women with postpartum psychosis (Nager et al., 2008; Paffenbarger, 1961; Paffenbarger & McCabe, 1966; Videbech & Gouliaev, 1995). Some studies found that a higher maternal age increased the risk of developing postpartum psychosis (Nager et al., 2005; Valdimarsdóttir et al., 2009). Incidentally, a higher maternal age may also be related to experiencing more complications related to pregnancy and delivery (Luke & Brown, 2007).

In summary, certain sociodemographic and obstetric factors are associated with postpartum psychosis. The aim of this chapter is to explore the sociodemographic background information, medical and obstetric history, and the history of stressful life events and clinical measures in our sample in order to present a detailed description of the study population and a tentative comparison to previous

epidemiological studies. Furthermore, the results discussed in this chapter will be used to assess the influence of certain clinical measures as potential confounders on cognitive, emotional, and neuroimaging processes in the following chapters.

3.2 Methods

The methods are described in chapter 2. For the combined analyses participants were split into “at risk” (N=25) and healthy control (N=21) groups as defined in chapter 2. For subsequent analyses, the “at risk” group was split into two sub groups; see section 3.3 where the results are presented.

3.3 Results

In the following section, psychiatric diagnoses, sociodemographic information, medical and obstetric history, nicotine, caffeine, cannabis, alcohol and other drugs of abuse consumption and clinical scales will be reported.

3.3.1 *Psychiatric diagnoses and clinical outcome*

The complete “at risk” group included 25 women who had either a previous diagnosis of bipolar disorder (N=14), schizoaffective disorder (bipolar type) (N=2), postpartum psychotic episodes only (N=8), a family history of postpartum psychosis (N=1) and healthy controls (N=21) according to the SCID. In order to confirm the diagnoses, clinical notes were also reviewed. No woman in the healthy control group had a current psychiatric diagnosis. For an overview of diagnoses see Table 3.1.

Table 3.1 Psychiatric diagnoses in the “at risk” group

N=14	Bipolar disorder
N=2	Schizoaffective disorder
N=8	Postpartum psychosis
N=1	First-degree family history of postpartum psychosis
N=25	Total

As described in the section on the inclusion criteria in the methods chapter, women were identified when either pregnant or within the first year after delivery. However, all assessments took place after delivery, and in the case of women who had a postpartum episode after this (i.e. the most recent) delivery, assessments took place when the woman was well enough to be approached, as indicated by the responsible clinician. Assessments took place in a range of 3-43 weeks after the most recent delivery.

For further analyses, the “at risk” group was split into two sub groups (sub group analysis). The “NPE” group consisted of 12 women who had non-postpartum episodes only (10 diagnosed with bipolar disorder and two with schizoaffective) and were “at risk” but had never developed postpartum psychosis. No woman in this group had developed postpartum psychosis following this pregnancy, or developed any other form of mental or physical illness after this pregnancy. The woman with a family history of postpartum psychosis was excluded from further analyses as her diagnosis was not suitable for the sub group comparison.

The “PE” group consisted of 12 women who had experienced at least one postpartum psychotic episode in their life, either with a previous pregnancy or with this pregnancy. Of this group, four women had experienced postpartum and non-postpartum episodes (all four had a history of bipolar disorder) and eight women had suffered postpartum episodes only. Out of the 12 women in this PE group, nine women had had postpartum psychosis following this delivery and three women have had postpartum psychosis with a previous delivery, but did not develop an episode after this pregnancy. Of the nine women who had developed postpartum psychosis following this delivery, five were diagnosed with a mood episode (two with depression with psychotic features and three with mania with psychotic features) and four with a brief psychotic episode. All women were diagnosed with postpartum psychosis according to the DSM-IV and this was cross-checked with the responsible clinician when possible. For an overview see Table 3.2.

Table 3.2 Diagnoses of the women according to sub groups

N =12	Diagnoses of women with NPE
N=10	Bipolar disorder
N=2	Schizoaffective disorder
N=12	Diagnoses of women with PE
N=4	Bipolar disorder and postpartum psychosis
N=8	Postpartum psychosis

Table 3.2 NPE=Non-postpartum episodes, PE=Postpartum episodes

3.3.2 Combined group analysis (CGA)

In the following section the “at risk” group as a whole will be compared to healthy controls.

3.3.2.1 Comorbidity (CGA)

Two women in the “at risk” group were also diagnosed with current anxiety disorder and two had a past history of anxiety disorder. One woman had a life-time diagnosis of anxiety and somatoform disorder, one a past history of an eating disorder (bulimia) and the woman with the family history of postpartum psychosis had suffered a depressive episode in the past. Of the healthy controls, two had a past diagnosis of an eating disorder and one had suffered a depressive episode in the past. However, none of the healthy controls had ever received prescribed medication for any of these conditions.

3.3.2.2 Sociodemographic Information (CGA)

Please refer to Table 3.3 and Table 3.4 for all relevant statistics in this section. Women did not significantly differ in age (age range 22–41 years), although there was a trend towards the healthy control group being older. There were no significant group differences between women “at risk” and healthy controls in terms of place of birth and childhood (until age 17), first language, or ethnicity. In both groups, approximately two-thirds of the women were born or spent the majority of their childhood in the United Kingdom and approximately 80% of the women spoke English as their first language.

There were no significant differences in marital status or partnership longevity between groups. Women did not significantly differ in their level of qualification or

employment status. There were also no differences in handedness between women. Groups did not differ regarding women being in a relationship with the biological father of the baby. There was a significant difference in the paternal ethnicity between groups, with more Caucasian partners in the healthy control group compared to the “at risk” group. One father’s ethnicity was unknown. For an overview of all ethnicities included in the study see Table 3.5. Partners in both groups had a high employment rate.

Table 3.3 Age and partnership longevity in years (CGA)

Groups	“at risk” M (SD)	HC M (SD)	Statistics
Age in years (N=46)	32.24 (4.68)	35 (4.53)	$z=-1.93$, $p=.053$
Partnership longevity in years (N=43)	7.05 (5.01)	8.05(4.19)	$z=-.87$, $p=.38$

Table 3.3 “at risk”=“at risk” group. HC=healthy control group. M=mean. SD=standard deviation.

Table 3.4 Sociodemographic information (CGA)

Category	Subcategory	“at risk” N (%)	HC N (%)	Statistics (df, N)
Place of birth and childhood	Either in UK	16 (64)	14 (67)	$\chi^2(3,46)=.28$, $p=.96$, $p_{\text{exact}}=1$
	Both outside UK	9 (36)	7 (33)	
First language	English	20 (80)	17 (81)	$\chi^2(1,46)<.01$, $p=.94$, $p_{\text{exact}}=1$
	Other	5 (20)	4 (19)	
Ethnicity of mother	Caucasian	13 (52)	16 (76)	$\chi^2(1,46)=2.87$, $p=.09$, $p_{\text{exact}}=.13$
	Other	12 (48)	5 (24)	
Marital status	Married/cohabit.	19 (75)	18 (86)	$\chi^2(3,46)=2.71$, $p=.44$, $p_{\text{exact}}=.51$
	Single partner	3 (12)	3 (14)	
	Single no partner	3 (12)	0	
Qualifications of mother	Degree or diploma	17 (68)	18 (86)	$\chi^2(1,46)=1.97$, $p=.16$, $p_{\text{exact}}=.19$
	Other	11 (44)	3 (14)	
Employment status of mother	Employed	15 (60)	16 (76)	$\chi^2(1,46)=1.36$, $p=.24$, $p_{\text{exact}}=.35$
	Other	10 (40)	5 (24)	
Handedness	Right	24 (96)	18 (86)	$\chi^2(1,46)=1.52$, $p=.22$, $p_{\text{exact}}=.32$
	Left	1 (4)	3 (14)	
Current partner biological father	Yes	21 (84)	21 (100)	$\chi^2(1,46)=3.68$, $p=.06$, $p_{\text{exact}}=.11$
	No	4 (16)	0	
Ethnicity of father	Caucasian	14 (58)	19 (91)	$\chi^2(1,45)=5.92$, $p=.02$, $p_{\text{exact}}=.02$
	Other	10 (42)	2 (9)	
Employment of father	Employed	19 (86)	20 (95)	$\chi^2(1,43)=1.00$, $p=.32$, $p_{\text{exact}}=.61$
	Other	3 (14)	1 (5)	

Table 3.4 “at risk”=“at risk” group. HC=healthy control group. %=percentage of group. Df=degrees of freedom.

Table 3.5 Ethnicity (CGA)

	White			Asian / Asian British		Black			Chinese	Other	Total
	British	Irish	Other	Pakistani	Other	Caribbean	African	Other			
Maternal											
“at risk” group N (% of group)	6 (24)	1 (4)	6 (24)	2 (8)	1 (4)	2 (8)	3 (12)	1 (4)	1 (4)	3 (12)	25 (100)
healthy controls N (% of group)	12 (57)	0	4 (19)	0	0	2 (10)	0	0	1 (5)	2 (10)	21 (100)
Total N (% of total)	18 (39)	1 (2)	10 (22)	2 (4)	1 (2)	4 (9)	3(7)	1 (2)	2 (4)	5 (11)	46 (100)
Paternal											
“at risk” group N (% of group)	6 (25)	2 (8)	6 (25)	1 (4)	1 (4)	4 (16)	1 (4)	1 (4)	1 (4)	1 (4)	24 (100)
healthy controls N (% of group)	15 (71)	0	4 (19)	0	0	1 (5)	1 (5)	0	0	0	21 (100)
Total N (% of total)	21(47)	2 (4)	10 (22)	1 (2)	1 (2)	5 (11)	2 (4)	1 (2)	1 (2)	1 (2)	45 (100)

3.3.2.3 Medication (CGA)

As defined in the inclusion criteria, none of the healthy controls took any prescribed medication. Eighteen women in the “at risk” group took prescribed medication at the time of the MRI scan. Among these, five had started treatment before pregnancy and 10 women after delivery. For three women the exposure in days was unknown. Of the “at risk” women taking antipsychotic medication (N=14), eight women were taking olanzapine, four were taking quetiapine, one was taking risperidone and one was taking haloperidol. Three women were taking antidepressants and one woman was taking benzodiazepines. For 12 women we were able to calculate the mean dose in chlorpromazine equivalents, which was 304mg per day (SD=252) based on Woods (2003). For 15 women we calculated the mean number of days of exposure, which was 246 days (SD=265). Two women were additionally taking mood stabilisers (one lithium valproate and one valproate semisodium). For an overview see Table 1 in Appendix B. There was no significant group difference between the “at risk” group and healthy controls in taking over-the-counter medication (e.g. multivitamins, fish oil, nicotine gum, contraceptive pill or paracetamol) at the time of the MRI scan ($\chi^2(1,46)=.64$, $p=.43$, $p_{\text{exact}}=.55$). In the “at risk” group 36% and in the healthy control group 48% were taking over-the-counter medication.

3.3.2.4 Medical and obstetric history (CGA)

Please refer to Table 3.6 and Table 3.7 for all relevant statistics in this section. Women were matched for the number of weeks after delivery. There was a trend for women at risk of postpartum psychosis to experience more problems during pregnancy/delivery (such as infection from a caesarean section or postpartum haemorrhage) and breastfeeding (e.g. not latching on) than healthy controls. There was a significant difference between groups in term of breastfeeding as women in the “at risk” group used formula more often than healthy controls. There was no significant difference in maternal parity between the “at risk” group and the healthy controls. There was also no difference in the number of previous pregnancies that did not result in a live birth, due to either termination of pregnancy or miscarriage. Both groups had a similar first onset of menarche. Nineteen women had already had their first menstrual cycle after their recent delivery by the time of the MRI scan and there

was no significant difference between groups. There was a strong tendency for more women in the “at risk” group to be classified as obese compared to healthy controls; this was according to the Body Mass Index classification (World Health Organisation).

Table 3.6 Weeks after delivery and onset of menarche (CGA)

Groups	“at risk” M (SD)	HC M (SD)	Statistics
Weeks after delivery (N=46)	16.76 (11.05)	14.43 (10.59)	$z=-1.08$, $p=.27$
Onset of menarche (N=46)	12.48 1.72	12.72 1.95	$z=-1.01$, $p=.32$

Table 3.6 “at risk”=“at risk” group. HC=healthy control group. M=mean. SD=standard deviation.

Table 3.7 Medical and obstetric history (CGA)

Category	Subcategory	“at risk” N (%)	HC N (%)	Statistics (df, N)
Problems during pregnancy/delivery	Yes	10 (40)	3 (14)	$\chi^2(1,46)=3.72$, $p=.05$, $p_{\text{exact}}=.09$
	No	15 (60)	18 (86)	
Problems during breastfeeding	Yes	9 (36)	3 (14)	$\chi^2(1,46)=2.79$, $p=.10$, $p_{\text{exact}}=.18$
	No	16 (64)	18 (86)	
Feeding	Breast only	7 (28)	11 (52)	$\chi^2(2,46)=8.03$, $p=.02$, $p_{\text{exact}}=.02$
	Formula	12 (48)	2 (10)	
	Mixed	6 (24)	8 (38)	
Parity	1 child	14 (56)	14 (67)	$\chi^2(2,46)=.99$, $p=.61$, $p_{\text{exact}}=.69$
	2 children	8 (32)	4 (19)	
	=>3 children	3 (12)	3 (14)	
Termination / miscarriage	Yes	15 (62)	11 (52)	$\chi^2(1,45)=.47$, $p=.49$, $p_{\text{exact}}=.56$
	No	9 (38)	10 (48)	
Menstrual cycle after recent delivery	Yes	11 (44)	8 (38)	$\chi^2(1,46)=.16$, $p=.68$, $p_{\text{exact}}=.77$
	No	14 (56)	13 (62)	
BMI classification	Normal: 18-25	8 (33)	7 (35)	$\chi^2(2,44)=5.99$, $p=.05$, $p_{\text{exact}}=.05$
	Overweight: 25-30	8 (33)	12 (60)	
	Obese:>30	8 (33)	1 (5)	

Table 3.7 “at risk”=“at risk” group. HC=healthy control group. %=percentage of group. Df=degrees of freedom.

3.3.2.5 Nicotine, caffeine, cannabis, alcohol and other drugs of abuse (CGA)

Please refer to Table 3.8 and Table 3.9 for all relevant statistics for this section. There were no significant differences between the “at risk” group and healthy controls in smoking history before pregnancy or current smoking (including during pregnancy and breastfeeding) or in coffee, tea or alcohol consumption at the time of the MRI scan.

There were also no significant differences between the two groups regarding the previous use of cannabis (i.e. whether women had ever tried cannabis and the mean duration of smoking cannabis). However, there was a significant difference between

the two groups in terms of frequency of cannabis use during the time of their highest use in the past, with the “at risk” women smoking cannabis more frequently than healthy controls. There was also a strong trend towards a group difference concerning the amount of cannabis used during their time of highest use with the “at risk” group using a higher amount than healthy controls. There was no significant difference between groups concerning the types of cannabis (hash, herbal cannabis or skunk) used ($\chi^2(3,32)=2.69$, $p=.44$, $p_{\text{exact}}=.53$). Only two women in the “at risk” group were still smoking cannabis at the time of the study.

Groups differed significantly concerning past alcohol and substance abuse. None of the healthy controls had a history of alcohol or substance abuse, but 32% of the “at risk” group did. Three women in the “at risk” group suffered from past alcohol abuse disorder, three women from past alcohol and substance abuse disorder and two women had a history of substance abuse only.

Table 3.8 Nicotine, caffeine, cannabis, alcohol and other drugs of abuse (CGA)

Category	Subcategory	“at risk” N (%)	HC N (%)	Statistics (df, N)
Smoking history before pregnancy	Yes	15 (60)	14 (67)	$\chi^2(1,46)=.22$, $p=.64$, $p_{\text{exact}}=.76$
	No	10 (40)	7 (33)	
Current smoking	Yes	6 (24)	1 (5)	$\chi^2(1,46)=3.27$, $p=.07$, $p_{\text{exact}}=.11$
	No	19 (76)	20 (5)	
	Never	12 (48)	5 (24)	
	Monthly or less	5 (20)	3 (14)	
Current alcohol use	2-4 times per month	6 (24)	8 (38)	$\chi^2(3,46)=4.64$, $p=.20$, $p_{\text{exact}}=.21$
	2-3 times per week	2 (8)	5 (23)	
Cannabis use during life-time	Yes	16 (67)	16 (76)	$\chi^2(1,45)=.49$, $p=.48$, $p_{\text{exact}}=.53$
	No	8 (33)	5 (24)	
Frequency of cannabis use/highest use	On a daily basis	9 (56)	3 (19)	$\chi^2(4,32)=10.81$, $p=.03$, $p_{\text{exact}}=.02$
	Less than daily	7 (44)	13 (81)	
Amount of cannabis used/highest use	1 joint	6 (37)	12 (75)	$\chi^2(2,32)=5.71$, $p=.06$, $p_{\text{exact}}=.06$
	2 or more joints	10 (63)	4 (25)	
Past alcohol or substance abuse	Yes	8 (32)	0	$\chi^2(3,46)=8.14$, $p<.04$, $p_{\text{exact}}=.02$
	No	17 (68)	21 (100)	

Table 3.8 “at risk”=“at risk” group. HC=healthy control group. %=percentage of group. Df=degrees of freedom.

Table 3.9 Past smoking, cannabis, coffee and tea consumption (CGA)

Groups	“at risk” M (SD)	HC M (SD)	Statistics
Number of cigarettes per day during highest use (N=29)	10.35 (6.31)	6.17 (6.98)	$z=-1.63$, $p=.11$
Past duration smoking cannabis (years) (N=28)	8.46 (5.77)	6.53 (5.23)	$z=-1.04$, $p=.30$
Coffee (cups per week) (N=46)	5.04 (8.21)	3.48 (4.08)	$z=-.89$, $p=.37$
Tea (cups per week) (N=46)	10.68 (10.89)	12.57 (13.76)	$z=-.22$, $p=.82$

Table 3.9 “at risk”=“at risk” group. HC=healthy control group. M=mean. SD=standard deviation.

3.3.2.6 Clinical assessments (CGA)

3.3.2.6.1 Life event scales and family history (CGA)

Please refer to Table 3.10 for all relevant statistics in this section. More women in the “at risk” group had experienced stressful life events (e.g. financial loss or being a victim of violence) during the previous six months compared to healthy controls. Similarly, more women in the “at risk” group had experienced intrusive life events (e.g. abuse or being a victim of violence) during their life-time compared to the healthy control group.

There was no significant difference between the “at risk” and the healthy control group concerning the severity of family arrangements (i.e. having had more than three family arrangements up until the age of 17 years) according the CECA- Q. However, there was a significant difference between the two groups concerning sexual and physical abuse. Women “at risk” reported more sexual and physical abuse than healthy controls. There was also a significant difference between the “at risk” group and healthy controls concerning the number of first-degree relatives that were diagnosed with a psychiatric illness. More women in the “at risk” group had a first-degree relative affected by a psychiatric illness than women in the healthy control group (also see Table 3 in Appendix C).

Table 3.10 Life event scales and family history (CGA)

Category	Subcategory	“at risk” N (%)	HC N (%)	Statistics (df, N)
Stressful life events/ past 6 months	Yes	13 (52)	4 (19)	$\chi^2(1,46)=5.32$,
	No	12 (48)	17 (81)	$p=.02$, $p_{\text{exact}}=.03$
Intrusive life events /life-time	Yes	19 (76)	9 (43)	$2(1,46)=5.26$,
	No	6 (24)	12 (57)	$p=.02$, $p_{\text{exact}}=.03$
Family arrangements	Less than 3	17 (68)	17 (81)	$\chi^2(1,46)=.99$,
	More than 3	8 (32)	4 (19)	$p=.32$, $p_{\text{exact}}=.50$
	No experiences	14 (58)	20 (95)	
Physical and sexual abuse experiences	Physical abuse	6 (25)	1 (5)	$\chi^2(3,45)=8.47$,
	Sexual abuse	1 (4)	0	$p=.04$, $p_{\text{exact}}=.02$
	Both	3 (13)	0	
Psychiatric illness in first-degree relative	Yes	15 (63)	3 (15)	$(\chi^2(1,44)=10.18$,
	No	9 (37)	17 (85)	$p<.01$, $p_{\text{exact}}<.01$)

Table 3.10 “at risk”=“at risk” group. HC=healthy control group. %=percentage of group. Df=degrees of freedom.

3.3.2.6.2 Assessment of functioning (CGA)

Please refer to Table 3.11 for all relevant statistics in this section. The GAF scores of the “at risk” group were significantly lower than those of the healthy controls both at the time of the MRI scan and during the previous year. Women were also evaluated at the time of the MRI scan according to the CGI. For an overview see Table 3.12.

Table 3.11 Assessment of functioning (CGA)

Groups	“at risk” M (SD)	HC M (SD)	Statistics
GAF scores (current) (N=46)	76.64 (17.06)	99.57 (1.96)	$z=-5.57, p<.01$
Highest GAF score during previous year (N=46)	88.52 (16.40)	99.76 (1.09)	$z=-3.51, p<.01$

Table 3.11 “At risk”=“at risk” group. HC=healthy control group. M=mean. SD=standard deviation.

Table 3.12 Clinical Global Impression (CGA)

Groups	“At risk” N (%)	HC N (%)	Total N (%)
Normal, not at all ill	1 (4)	21 (100)	22 (48)
Borderline mentally ill	5 (20)	NA	5 (11)
Mildly ill	7 (28)	NA	7 (15)
Moderately ill	11 (44)	NA	11 (24)
Markedly ill	1 (4)	NA	1 (2)
Total	25 (100)	21 (100)	46 (100)

Table 3.12 “at risk”=“at risk” group. HC=healthy control group. %=percentage of group.

3.3.2.6.3 Mood and symptom scales (CGA)

Please refer to Table 3.13 for all relevant statistics in this section. In comparison to healthy controls, the “at risk” group scored significantly higher on all mood and symptom scales including the Ham-D, BDI, YMRS, and PANSS.

Table 3.13 Mood and symptom scales (CGA)

Groups	“at risk” M (SD)	HC M (SD)	Statistics
Ham-D	6.56 (3.03)	2.05 (3.0)	$z=-3.32, p<.01$
BDI	9.28 (8.67)	3.05 (4.07)	$z=-2.84, p<.01$
YMRS	1.80 (2.11)	.52 (.82)	$z=-2.51, p=.01$
PANSS (positive)	8.44 (2.45)	7.05 (.22)	$z=-3.05, p<.01$
PANSS (negative)	8.56 (3.54)	7 (0)	$z=-2.81, p<.01$
PANSS (GPS)	21.32 (5.24)	16.90 (1.95)	$z=-3.87, p<.01$
PANSS (total)	38.32 (7.29)	30.95 (2.01)	$z=-4.31, p<.01$

Table 3.13 “at risk”=“at risk” group. HC=healthy control group. M=mean. SD=standard deviation.

3.3.2.6.4 Stress, anxiety and sleep scales (CGA)

Please refer to Table 3.14 for all relevant statistics in this section. Women in the “at risk” group scored higher on all scales assessing state and trait anxiety, perceived stress, and sleep.

Table 3.14 Stress, anxiety and sleep scales (CGA)

Groups	“at risk” M (SD)	HC M (SD)	Statistics
SAI	34.64 (12.39)	26.19 (6.79)	$z=-2.43, p=.01$
TAI	42.52 (13.32)	30.3 (8.91)	$z=-3.12, p<.01$
PSS	17.36 (7.46)	8.48 (7.32)	$t(44)=-4.06, p<.01$
AIS	5.60 (4.59)	3.33 (4.71)	$z=-2.26, p=.02$

Table 3.14 “at risk”=“at risk” group. HC=healthy control group. M=mean. SD=standard deviation.

3.3.2.7 Cognitive assessments

Women did not differ in their full scale IQ as predicted by the WTAR (women “at risk”, Mean (M)=101.75, SD=11.44; healthy controls, M=109.44, SD=13.36 $z=-1.22, p=.22$).

3.3.3 Sub group analysis (SGA)

In the following section women with non-postpartum episodes and postpartum episodes are compared to each other and healthy controls.

3.3.3.1 Comorbidity (SGA)

Two women in the NPE group were diagnosed with a current anxiety disorder; two women had a past history of anxiety disorder and one a past history of an eating disorder (bulimia). One woman in the PE group had a life-time diagnosis of anxiety and somatoform disorder.

3.3.3.2 Number of episodes, age of onset and length of illness (SGA)

Please refer to Table 3.15 and Table 3.16 for all relevant statistics in this section. Length of illness was determined based on the interviews. Women were asked when they had experienced their first episode (year and age), when they had seen a psychologist or psychiatrist for the first time, and when they had received medication

for the first time. This information was cross-checked with the clinical notes for validation and if possible with the responsible psychiatrist. Length of illness was calculated in years. When we compared the length of illness for women who had experienced more than one episode, we did not find any significant difference between women in the NPE and PE groups. There was a significant difference in the number of mood or psychotic episodes between the NPE and PE groups, as more women in the NPE group had a higher number of episodes than in the PE group. Women suffering from non-postpartum episodes only also had an earlier onset of illness than women with a postpartum onset.

Table 3.15 Age of onset and length of illness (SGA)

Groups	NPE M (SD)	PE M (SD)	Statistics
Age of onset in years (N=22)	21.42 (4.75)	27 (6.28)	$z=-2.54$, $p=.01$
Length of illness in years (N=18)	9.50 (6.61)	8.88 (7.16)	$z=-.46$, $p=.64$

Table 3.15 NPE=group with non-postpartum episodes. PE=group with postpartum episodes. M=mean. SD=standard deviation.

Table 3.16 Number of Episodes (SGA)

Groups	NPE N (%)	PE N (%)	Total N (%)	Statistics (df, N)
1 episode	0	4 (33)	4 (17)	$\chi^2(4,24)=10.12$, $p=.04$, $p_{\text{exact}}=.01$
2 episodes	2 (17)	4 (33)	6 (25)	
3 episodes	1 (8)	1 (8)	2 (8)	
4 episodes	0	1 (8)	1 (4)	
>5 episodes	9 (75)	2 (17)	11 (46)	
Total	12 (100)	12 (100)	24 (100)	

Table 3.16 NPE=group with non-postpartum episodes. PE=group with postpartum episodes. %=percentage of group. Df=degrees of freedom.

3.3.3.3 Sociodemographic Information (SGA)

Please refer to Table 3.17 and Table 3.18 for all relevant statistics in this section. Women did not significantly differ in age. There were also no significant group differences between the NPE, PE, and healthy control groups for place of birth, first language, or ethnicity. Groups did not differ in handedness. There were no significant differences in marital status or partnership longevity between groups. There were no significant differences between groups in level of qualifications or employment status. However, fewer women in the NPE group were in a romantic relationship with the biological father of the baby compared to healthy controls ($\chi^2(1,33)=5.78$, $p=.02$, $p_{\text{exact}}=.04$). This was not significant following Bonferroni correction of $\alpha=.016$.

There was also a significant difference between the NPE and healthy control groups concerning the paternal ethnicity following pairwise comparison with Bonferroni correction as more women in the healthy control group were with a Caucasian partner ($\chi^2(1,32)=7.80$, $p<.01$ $p_{\text{exact}}=.01$). There was a significant difference between groups concerning partners' employment rates as fewer partners in the NPE group were employed compared to both the PE and healthy control groups ($\chi^2(1,21)=4.67$, $p=.03$ $p_{\text{exact}}=.06$; $\chi^2(1,30)=4.45$, $p=.04$ $p_{\text{exact}}=.07$, respectively). These pairwise comparisons were not significant following Bonferroni correction of $\alpha=.016$. All other pairwise comparisons were $p>.05$ without Bonferroni correction.

Table 3.17 Age and partnership longevity in years (SGA)

Groups	NPE M (SD)	PE M (SD)	HC M (SD)	Statistics (df, N)
Age in years	31.17 (5.98)	33.25 (4.82)	35 (4.53)	$\chi^2(2,45)=3.84$, $p=.15$
Partnership longevity in years	4.89 (3.62)	8.92 (5.47)	8.05(4.19)	$\chi^2(2,42)=4.09$, $p=.13$

Table 3.17 NPE=group with non-postpartum episodes. PE=group with postpartum episodes. M=mean. SD=standard deviation. Df=degrees of freedom.

Table 3.18 Sociodemographic information (SGA)

Category	Subcategory	NPE N (%)	PE N (%)	HC N (%)	Statistics (df, N)
Place of birth and childhood	Either in UK	9 (75)	6 (50)	14 (67)	$\chi^2(6,45)=4.88$, $p=.56$, $p_{\text{exact}}=.66$
	Both outside UK	3(25)	6 (50)	7 (33)	
First language	English	11 (92)	8 (67)	17 (81)	$\chi^2(2,45)=2.37$, $p=.31$, $p_{\text{exact}}=.32$
	Other	1 (8)	4 (33)	4 (19)	
Ethnicity of mother	Caucasian	5 (42)	7 (58)	16 (76)	$\chi^2(2,45)=3.98$, $p=.14$, $p_{\text{exact}}=.15$
	Other	7 (58)	5 (42)	5 (24)	
Marital status	Married/Cohabit.	7 (58)	11 (92)	18 (86)	$\chi^2(6,45)=9.69$, $p=.14$, $p_{\text{exact}}=.28$
	Single partner	2 (17)	1 (8)	3 (14)	
	Single no partner	3 (25)	0	0	
Qualifications of mother	Degree or diploma	6 (50)	10 (83)	18 (86)	$\chi^2(2,45)=5.81$, $p=.06$, $p_{\text{exact}}=.09$
	Other	6 (50)	2 (17)	3 (14)	
Employment status of mother	Employed	6 (50)	8 (67)	16 (76)	$\chi^2(2,45)=2.36$, $p=.31$, $p_{\text{exact}}=.29$
	Other	6 (50)	4 (33)	5 (24)	
Handedness	Right	12 (100)	11 (92)	18 (86)	$\chi^2(2,45)=1.93$, $p=.38$, $p_{\text{exact}}=.57$
	Left	0	1 (8)	3 (24)	
Current partner biological father	Yes	9 (75)	11 (92)	21 (100)	$\chi^2(2,45)=5.89$, $p=.05$ $p_{\text{exact}}=.04$
	No	3 (25)	1 (8)	0	
Ethnicity of father	Caucasian	5 (46)	8 (67)	19 (91)	$\chi^2(2,44)=7.68$, $p=.02$, $p_{\text{exact}}=.02$
	Other	6 (54)	4 (33)	2 (9)	
Employment of father	Employed	6 (67)	12 (100)	20 (95)	$\chi^2(2,42)=7.73$, $p=.02$, $p_{\text{exact}}=.03$
	Other	3 (33)	0	1 (5)	

Table 3.18 "NPE=group with non-postpartum episodes. PE=group with postpartum episodes. %=percentage of group. Df=degrees of freedom.

3.3.3.4 Medication (SGA)

Please refer to Table 3.19 and Table 3.20 for all relevant statistics for this section. There was no significant difference between the NPE and PE groups in terms of how many women used prescribed medication at the time of the MRI scan. Four women in the NPE group had started treatment before pregnancy and one after delivery. One woman in the PE group started treatment before delivery and nine after pregnancy. For three women the exposure in days was unknown. Of the women in the NPE group taking antipsychotic medication (N=5), two women took olanzapine, two quetiapine and one haloperidol. Of the women in the PE group taking antipsychotic medication (N=9), six women took olanzapine, two women took quetiapine and one woman took risperidone. One woman in the NPE group and one woman in the PE group were additionally taking mood stabilisers. For an overview see Table 2 in Appendix B. There was a significant difference between the NPE group and the PE group in terms of exposure in days, with women in the NPE group taking antipsychotic medication longer on average than the PE group. There was no significant difference between the NPE and PE groups in terms of mean dose in chlorpromazine equivalents at the time of the MRI scan (Woods, 2003).

Table 3.19 Prescribed medication at the time of the MRI scan I (SGA)

Groups	NPE N (%)	PE N (%)	Statistics (df, N)
Yes	7 (58)	11 (92)	$\chi^2(1,24)=3,56$, p=.06, p _{exact} =.16
No	5 (42)	1 (8)	

Table 3.19 NPE=group with non-postpartum episodes. PE=group with postpartum episodes. %=percentage of group. Df=degrees of freedom.

Table 3.20 Prescribed medication at the time of the MRI scan II (SGA)

Groups	NPE M (SD)	PE M (SD)	Statistics
Exposure in days (N=15)	484 (212)	127 (205)	$z=-2.45$, p=.01
Mean dose in chlorpromazine equivalents (mg per day) (N=12)	342 (225)	285 (276)	$z=-.43$, p=.67

Table 3.20 NPE=group with non-postpartum episodes. PE=group with postpartum episodes. M=mean. SD=standard deviation.

There was no significant group difference between women taking over-the-counter medication (e.g. multivitamins, fish oil, nicotine gum, contraceptive pill or paracetamol) at the time of the MRI scan ($\chi^2(2,45)=.64$, p=.73, p_{exact}=.80). In the NPE group 33%, in the PE group 42% and in the healthy control group 48% were taking over-the-counter medication.

3.3.3.5 Medical and Obstetric History (SGA)

Please refer to Table 3.21 and Table 3.22 for all relevant statistics for this section. There was no significant difference between groups for weeks after delivery. Women did not differ concerning problems during pregnancy/delivery or with breastfeeding. However, there was a significant difference between groups concerning the current feeding of the baby. Fewer women in the PE group were breastfeeding compared to healthy controls following Bonferroni correction ($\chi^2(2,33)=9.54$, $p<.01$, $p_{\text{exact}}=.01$). All other pairwise comparisons were $p>.05$ without Bonferroni correction.

All three groups had a similar onset of menarche and there were no differences between groups in women having had a first menstrual cycle after the recent delivery by the time of the MRI scan or in maternal parity. There were also no group differences in the number of previous pregnancies that did not result in a live birth, due to either a termination of pregnancy or miscarriage. Finally, there was no significant difference between groups according the Body Mass Index classification (World Health Organisation).

Table 3.21 Weeks after delivery and onset of menarche (SGA)

Groups	NPE M (SD)	PE M (SD)	HC M (SD)	Statistics (df, N)
Weeks after delivery	13 (6.28)	21 (13.75)	4.43 (10.59)	$\chi^2(2,45)=2.31$, $p=.31$
Onset of menarche	13 (1.54)	12.33 (2.3)	12.48 (1.7)	$\chi^2(2,45)=.98$, $p=.61$

Table 3.21 NPE=group with non-postpartum episodes. PE=group with postpartum episodes. M=mean. SD=standard deviation. Df=degrees of freedom.

Table 3.22 Medical and obstetric history (SGA)

Category	Subcategory	NPE N (%)	PE N (%)	HC N (%)	Statistics (df, N)
Problems during pregnancy/delivery	Yes	6 (50)	4 (33)	3 (14)	$\chi^2(2,45)=4.89$, $p=.09$, $p_{\text{exact}}=.09$
	No	6 (50)	8 (67)	18 (86)	
Problems during breastfeeding	Yes	4 (33)	5 (42)	3 (14)	$\chi^2(2,45)=3.30$, $p=.19$, $p_{\text{exact}}=.20$
	No	8 (67)	7 (58)	18 (86)	
Feeding	Breast only	4 (33)	2 (17)	11 (52)	$\chi^2(4,45)=9.72$, $p=.05$, $p_{\text{exact}}=.04$
	Formula	5 (42)	7 (58)	2 (10)	
	Mixed	3 (25)	3 (25)	8 (38)	
Parity	1 child	7 (58)	6 (50)	14 (67)	$\chi^2(4,45)=1.56$, $p=.82$, $p_{\text{exact}}=.80$
	2 children	4 (33)	4 (33)	4 (19)	
	=>3 children	1 (8)	2 (25)	3 (14)	
Termination / miscarriage	Yes	7 (58)	7 (6)	11 (52)	$\chi^2(2,44)=.39$, $p=.82$, $p_{\text{exact}}=.92$
	No	5 (42)	4 (36)	10 (48)	
Menstrual cycle after recent delivery	Yes	5 (42)	6 (50)	8 (38)	$\chi^2(2,45)=.45$, $p=.80$, $p_{\text{exact}}=.92$
	No	7 (58)	6 (50)	13 (62)	
BMI classification	Normal: 18-25	5 (42)	3 (27)	7 (35)	$\chi^2(4,43)=7.18$, $p=.13$, $p_{\text{exact}}=.10$
	Overweight: 25-30	3 (25)	4 (36)	12 (60)	
	Obese:>30	4 (33)	4 (36)	1 (5)	

Table 3.22 NPE=group with non-postpartum episodes. PE=group with postpartum episodes. %=percentage of group. Df=degrees of freedom.

3.3.3.6 Nicotine, caffeine, cannabis, alcohol and other drugs of abuse (SGA)

Please refer to Table 3.23 and Table 3.24 for all relevant statistics in this section. There was no difference between the NPE, PE and healthy control groups in smoking history before pregnancy. However, women differed in the number of cigarettes smoked during the period of highest use. Women in the NPE group had smoked on average more cigarettes than healthy controls ($z=-2.06$, $p=.04$) and the PE group ($z=-2.04$, $p=.04$). However these pairwise comparisons were not significant following Bonferroni correction ($\alpha=.016$). There was no difference between groups in terms of current smoking (i.e. including during pregnancy and breastfeeding). There were also no significant group differences in coffee, tea or alcohol consumption at the time of the MRI scan.

There was a significant group difference regarding previous use of cannabis. More women in the NPE group had tried cannabis in their life-time compared to the PE group ($\chi^2(1,23)=6.14$, $p=.01$, $p_{\text{exact}}=.03$); however, this did not remain significant following Bonferroni correction of $\alpha=.016$. There was no significant difference between groups concerning the mean duration of smoking cannabis in years, the frequency or amount of cannabis used during the period of highest use, or the type of cannabis (hash, herbal cannabis or skunk) used ($\chi^2(6,31)=5.19$, $p=.52$, $p_{\text{exact}}=.49$).

Only two women in the NPE group were still smoking cannabis at the time of the MRI scan.

There was a significant difference between groups concerning past alcohol and substance abuse, as none of the healthy controls, but 33% of the women in the NPE and PE groups had a history of alcohol or substance abuse ($\chi^2(2,33)=7.96$, $p=.02$, $p_{\text{exact}}=.01$; ($\chi^2(3,33)=7.96$, $p=.05$, $p_{\text{exact}}=.01$). This remained significant following Bonferroni correction ($\alpha=.016$). Of the NPE group two women had a history of alcohol abuse and two women had a history of alcohol and substance abuse. In the PE group one woman had a history of alcohol abuse, two of substance abuse and one of alcohol and substance abuse. All other pairwise comparisons were $p>.05$ without Bonferroni correction.

Table 3.23 Nicotine, caffeine, cannabis, alcohol and other drugs of abuse (SGA)

Category	Subcategory	NPE N (%)	PE N (%)	HC N (%)	Statistics (df, N)
Smoking history before pregnancy	Yes	9 (75)	5 (42)	14 (67)	$\chi^2(2,45)=3.17$, $p=.21$, $p_{\text{exact}}=.28$
	No	3 (25)	7 (58)	7 (33)	
Current smoking	Yes	3 (25)	2 (17)	1 (5)	$\chi^2(2,45)=2.86$, $p=.24$, $p_{\text{exact}}=.29$
	No	9 (75)	10 (83)	20 (5)	
Current alcohol use	Never	5 (42)	6 (50)	5 (24)	$\chi^2(6,45)=7.71$, $p=.26$, $p_{\text{exact}}=.22$
	Monthly or less	2 (17)	3 (25)	3 (14)	
	2-4 times per month	5 (42)	1 (8)	8 (38)	
	2-3 times per week	0	2 (17)	5 (23)	
Cannabis use during life-time	Yes	10 (91)	5 (42)	16 (76)	$\chi^2(2,44)=7.32$, $p=.03$, $p_{\text{exact}}=.04$
	No	1 (9)	7 (58)	5 (24)	
Frequency of cannabis use/highest use	On a daily basis	6 (60)	2 (40)	3 (19)	$\chi^2(8,31)=11.94$, $p=.15$, $p_{\text{exact}}=.11$
	Less than daily	4 (40)	3 (60)	13 (81)	
Amount of cannabis used/highest use	1 joint	4 (40)	2 (40)	12 (75)	$\chi^2(4,31)=6.06$, $p=.19$, $p_{\text{exact}}=.16$
	2 or more joints	6 (60)	3 (60)	4 (25)	
Past alcohol or substance abuse	Yes	4 (33)	4 (33)	0	$\chi^2(6,45)=13.51$, $p=.04$, $p_{\text{exact}}<.01$
	No	8 (67)	8 (67)	21 (100)	

Table 3.23 NPE=group with non-postpartum episodes. PE=group with postpartum episodes. %=percentage of group. Df=degrees of freedom.

Table 3.24 Past smoking, cannabis, coffee and tea consumption (SGA)

Groups	NPE M (SD)	PE M (SD)	HC M (SD)	Statistics (df, N)
Number of cigarettes per day during highest use	13.37 (6.54)	6 (1.58)	6.17 (6.98)	$\chi^2(2,28)=6.716$, p=.04
Past duration of smoking cannabis (years)	8.07 (6.3)	9 (5.61)	6.53 (5.23)	$\chi^2(2,28)=1.29$, p=.52
Coffee (cups per week)	5.42 (7.65)	5.08 (9.29)	3.48 (4.08)	$\chi^2(2,45)=.74$, p=.69
Tea (cups per week)	11.67 (12.18)	9.42 (10.34)	12.57 (13.76)	$\chi^2(2,45)=.12$, p=.94

Table 3.24 NPE=group with non-postpartum episodes. PE=group with postpartum episodes. M=mean. SD=standard deviation. Df=degrees of freedom.

3.3.3.7 Clinical assessments (SGA)

3.3.3.7.1 Life event scales and family history (SGA)

Please refer to Table 3.25 for all relevant statistics in this section. There was a trend level difference concerning the experience of stressful life events during the previous six months and intrusive life events over a life-time between groups, with more women in the NPE group having experienced stressful and intrusive life events. There was no significant difference between the NPE, PE, and the healthy control groups concerning the severity of family arrangements (i.e. having had more than three family arrangements up until the age of 17 years) according the CECA- Q.

However, there were significant differences between the three groups concerning sexual and physical abuse before the age 17, with the NPE group having higher rates of physical and sexual abuse than healthy controls ($\chi^2(3,33)=12.26$, $p<.01$, $p_{\text{exact}}<.01$). This remained significant following Bonferroni correction ($\alpha=.016$). There was also a significant difference between the NPE, PE and healthy control groups concerning the number of first-degree relatives that were diagnosed with a psychiatric illness. More women in the NPE group had first-degree relatives with a psychiatric illness compared to the PE group and healthy controls ($\chi^2(1,23)=7.99$, $p=.01$, $p_{\text{exact}}=.01$; $\chi^2(1,31)=16.79$, $p<.01$, $p_{\text{exact}}<.01$, respectively). These pairwise comparisons remained significant following Bonferroni correction ($\alpha=.016$). Also see Table 4 in Appendix C. All other pairwise comparisons were $p>.05$ without Bonferroni correction.

Table 3.25 Life event scales and family history (SGA)

Category	Subcategory	NPE N (%)	PE N (%)	HC N (%)	Statistics (df, N)
Stressful life events / past 6 months	Yes	7 (58)	6 (50)	4 (19)	$\chi^2(2,45)=6.28$, $p=.05$, $p_{\text{exact}}=.06$
	No	5 (42)	6 (50)	17 (81)	
Intrusive life events / life-time	Yes	10 (83)	8 (67)	9 (43)	$\chi^2(2,45)=5.52$, $p=.06$, $p_{\text{exact}}=.07$
	No	2 (17)	4 (33)	12 (57)	
Family arrangements	Less than 3	7 (58)	10 (83)	17 (81)	$\chi^2(2,45)=2.65$, $p=.27$, $p_{\text{exact}}=.34$
	More than 3	5 (42)	2 (17)	4 (19)	
Physical and sexual abuse experiences	No experiences	5 (42)	9 (82)	20 (95)	$\chi^2(6,44)=13.56$, $p=.04$, $p_{\text{exact}}<.01$
	Physical abuse	4 (33)	1 (9)	1 (5)	
	Sexual abuse	1 (8)	0	0	
	Both	2 (17)	1 (9)	0	
Psychiatric illness in first-degree relative	Yes	10 (91)	4 (33)	3 (15)	$\chi^2(2,43)=17.37$, $p<.01$, $p_{\text{exact}}<.01$
	No	1 (9)	8 (67)	17 (85)	

Table 3.25 NPE=group with non-postpartum episodes. PE=group with postpartum episodes. %=percentage of group. Df=degrees of freedom.

3.3.3.7.2 Assessment of functioning (SGA)

Please refer to Table 3.26 and Table 3.27 for all relevant statistics in this section. There was a significant difference between the GAF scores of the NPE, PE and healthy control groups, with both the NPE and PE group having lower scores than healthy controls following Bonferroni correction ($z=-5.31$, $p<.01$; $z=-4.59$, $p<.01$, respectively). This was similar for the highest mean GAF score during the previous year ($z=-3.91$, $p<.01$; $z=-2.67$, $p<.01$, respectively). Women were also evaluated at the time of the MRI scan according to the CGI and there was no significant difference between the NPE and PE groups. All other pairwise comparisons were $p>.05$ without Bonferroni correction.

Table 3.26 Assessment of functioning (SGA)

Groups	NPE M (SD)	PE M (SD)	HC M (SD)	Statistics (df, N)
GAF scores (current)	76.50 (15.23)	75.58 (19.57)	99.57 (1.96)	$\chi^2(2,45)=30.69$, $p<.01$
Highest GAF score / previous year	86.08 (15.01)	90 (18.46)	99.76 (1.09)	$\chi^2(2,45)=14.76$, $p<.01$

Table 3.26 NPE=group with non-postpartum episodes. PE=group with postpartum episodes. M=mean. SD=standard deviation. Df=degrees of freedom.

Table 3.27 Clinical Global Impression (SGA)

Groups	NPE N (%)	PE N (%)	HC N (%)	Total N (%)	Statistics (df, N)
Normal, not at all ill	1 (8)	0	21 (100)	22 (49)	$\chi^2(4,24)=4.10$, $p=.39$, $p_{\text{exact}}=.39$
Borderline mentally ill	2 (17)	2 (17)	NA	4 (9)	
Mildly ill	5 (42)	2 (17)	NA	7 (16)	
Moderately ill	4 (33)	7 (58)	NA	11 (24)	
Markedly ill	0	1 (8)	NA	1 (2)	
Total	12 (100)	12 (100)	21 (100)	45 (100)	

Table 3.27 NPE=group with non-postpartum episodes. PE=group with postpartum episodes. %=percentage of group. Df=degrees of freedom.

3.3.3.7.3 Mood and symptom scales (SGA)

Please refer to Table 3.28 for all relevant statistics in this section. The NPE and the PE groups scored significantly higher than healthy controls following Bonferroni correction on the Ham-D ($z=-2.69$, $p<.01$; $z=-2.63$, $p<.01$, respectively), the positive symptom scale ($z=-3.05$, $p<.01$; $z=-2.73$, $p<.01$, respectively), the negative symptom scale ($z=-2.36$, $p=.02$; $z=-3.15$, $p<.01$, respectively), the general pathology scale ($z=-2.68$, $p<.01$; $z=-3.87$, $p<.01$, respectively), the total score of the PANSS ($z=-3.16$, $p<.01$; $z=-4.19$, $p<.01$, respectively), and the BDI ($z=-2.33$, $p=.02$; $z=-2.16$, $p=.03$, respectively), although the difference on the BDI was not significant following Bonferroni correction ($\alpha=.016$). There was also a significant difference between the NPE, PE and healthy control groups on the YMRS, with the PE group having a higher score than healthy controls following Bonferroni correction ($z=-3.10$, $p<.01$). All other pairwise comparisons were $p>.05$ without Bonferroni correction.

Table 3.28 Mood and symptom scales (SGA)

Groups	NPE M (SD)	PE M (SD)	HC M (SD)	Statistics (df, N)
Ham-D	6.50 (5.94)	6.33 (5.94)	2.05 (3.0)	$\chi^2(2,45)=10.32$, $p=.01$
BDI	9.00 (8.07)	9.25 (9.87)	3.05 (4.07)	$\chi^2(2,45)=7.41$, $p=.03$
YMRS	1.67 (2.64)	2.08 (1.51)	.52 (.82)	$\chi^2(2,45)=9.39$, $p=.01$
PANSS (positive)	8.08 (1.78)	8.92 (3.06)	7.05 (.22)	$\chi^2(2,45)=9.81$, $p<.01$
PANSS (negative)	7.58 (1.08)	9.67 (4.85)	7 (0)	$\chi^2(2,45)=9.48$, $p<.01$
PANSS (GPS)	20.75 (5.31)	22.08 (5.50)	16.90 (1.95)	$\chi^2(2,45)=15.76$, $p<.01$
PANSS (total)	36.42 (5.96)	40.67 (8.24)	30.95 (2.01)	$\chi^2(2,45)=19.87$, $p<.01$

Table 3.28 NPE=group with non-postpartum episodes. PE=group with postpartum episodes. M=mean. SD=standard deviation. Df=degrees of freedom

3.3.3.7.4 Stress, anxiety and sleep scales (SGA)

Please refer to Table 3.29 for all relevant statistics in this section. The NPE and the PE groups had significantly higher scores than healthy controls on the TAI ($z=-2.14$, $p=.03$; $z=-2.81$, $p<.01$, respectively), although only the latter remained significant following Bonferroni correction ($\alpha=.016$). The NPE and the PE groups also had significantly higher scores than healthy controls on the PSS ($z=-2.4$, $p=.02$; $z=-3.25$, $p<.01$, respectively) although only the former remained significant following Bonferroni correction ($\alpha=.016$). Women in the PE group had a higher score than healthy controls on the SAI after Bonferroni correction ($\alpha=.016$) ($z=-2.55$, $p=.01$). The three groups did not differ on the Athens Insomnia Scale. All other pairwise comparisons were $p>.05$ without Bonferroni correction.

Table 3.29 Stress, anxiety and sleep scales (SGA)

Groups	NPE M (SD)	PE M (SD)	HC M (SD)	Statistics (df, N)
SAI	31 (10.07)	37.83 (14.33)	26.19 (6.79)	$\chi^2(2,45)=6.98$, $p=.03$
TAI	41 (14.55)	43.17 (12.96)	30.3 (8.91)	$\chi^2(2,45)=9.30$, $p=.01$
PSS	15.75 (8.60)	19 (6.45)	8.48 (7.32)	$\chi^2(2,45)=13.50$, $p<.01$
AIS	5.92 (5.29)	5.17 (4.15)	3.33 (4.71)	$\chi^2(2,45)=4.77$, $p=.09$

Table 3.29 NPE=group with non-postpartum episodes. PE=group with postpartum episodes. M=mean. SD=standard deviation. Df=degrees of freedom

3.3.3.8 Cognitive assessments (SGA)

Women did not differ in their full scale IQ as predicted by the WTAR (NPE group $M=104.20$, $SD=8.92$; PE group $M=98.44$, $SD=14.09$; healthy controls $M=109.44$, $SD=13.36$; $\chi^2(2,37)=1.82$, $p=.40$).

3.4 Discussion

This chapter describes the psychiatric diagnoses, sociodemographic characteristics, medical and obstetric history, nicotine, caffeine, cannabis and alcohol and drugs of abuse consumption of the participants as well as the clinical scales used in the current study. The main aims were to assess the clinical and sociodemographic characteristics of the participants and investigate in our study population the rates of certain features across groups such as primiparity, problems with delivery, low social

support or poor socioeconomic status that have been previously associated with postpartum psychosis. In the following section the results will be summarised and interpreted in the context of the existing literature. It is important to bear in mind that this chapter provides a series of exploratory analyses and that we -due to the low sample size in our study- did not specify any epidemiological hypotheses, but simply report on the clinical and sociodemographic characteristics of the women in this study. In order to assess a meaningful epidemiological sample, a much larger sample size would be required. Nevertheless, this chapter may give an insight into what the potential confounders for this study may be, and point to what factors may need to be taken into account in future investigations.

3.4.1 Clinical characteristics of the groups

It has been reported that women with postpartum psychosis seem to have a better prognosis in terms of number of relapses and time on medication than women who had additional or only non-postpartum episodes (Davidson & Robertson, 1985; Dean et al., 1989; Doucet et al., 2009; Nager et al., 2005; Serretti et al., 2006). The findings in our study that women in the NPE group had a higher number of mood or psychotic episodes compared to the PE group and an earlier age of onset seems to be in line with this finding. In addition, it has been found previously that women with postpartum psychosis have often attained higher functional levels before symptom onset compared to chronic illness (Sit et al., 2006). One possible reason for this may be a later illness onset, as also suggested by our data.

However, since episodes in this study have been assessed retrospectively, the possibility cannot be excluded that the women who have suffered recently from their first or second postpartum episode will develop more postpartum or non-postpartum relapses in the future. It is important to carry out prospective follow-up studies in order to address this issue. Two women in the NPE group had a current comorbidity of anxiety disorder and one woman in the PE group had a life-time diagnosis of anxiety and somatoform disorder. None of the healthy controls had ever received prescribed medication. Therefore, current or past psychiatric comorbidities were considered unlikely to be significant and were not included in further analysis. In the

current study the focus is on the evaluation of the medical and obstetric history and socioeconomic background of the participants.

3.4.2 Socioeconomic background

The groups did not significantly differ in age, although there was a non-significant trend that women in the healthy control group were older than women in the “at risk” group. This finding is not in line with other research studies, which showed that there is a higher risk for women with a higher maternal age to develop postpartum psychosis (Nager et al., 2005; Valdimarsdóttir et al., 2009). Our finding may simply reflect a greater willingness of more mature healthy mothers to take part in research compared to younger and maybe less experienced mothers. However, the actual mean age difference between the groups was small and the age range for all women was restricted to the years from 22 to 41. Therefore, we do not expect this difference to represent a confounder in the analyses.

There were no differences between groups for place of birth, first language, or ethnicity in the main or sub group analyses. In all groups, the majority of the women were born or spent the majority of their childhood (until the age of 17) in the United Kingdom and spoke English as their first language. There was a significant difference between groups concerning the paternal ethnicity, as there were more Caucasian partners in the control group than in the “at risk” group, specifically in the NPE group. It is possible that the difference in the partners’ ethnicity may be associated with a difference in socioeconomic status (Kendell et al., 1976; Paffenbarger, 1961). However, as the difference was found for the NPE group, it does not confirm that a lower socioeconomic status is associated with the development of postpartum psychosis, as has previously been suggested (Kirpinar et al., 1999; Nager et al., 2006; Nager et al., 2012). In addition, our population as a whole was recruited from a relatively deprived area and is therefore likely to be matched on the socioeconomic background.

In addition, the groups did not differ in their marital status or the stability of their relationships. The majority of women were married or cohabiting. Even though a small amount of the women were not living with the father of the baby, most women in all the groups were in a stable relationship with a partner taking on the father role.

This finding is different to previous suggestions that postpartum psychosis is associated with “being single” or lacking social support due to a poor partner relationship (Bilszta et al., 2010; Cheetham et al., 1981; Kendell et al., 1987; Kendell, Rennie, et al., 1981; Marks et al., 1992; Nager et al., 2005, 2006; Paffenbarger, 1961; Paffenbarger & McCabe, 1966). Nonetheless, due to the small sample size it is difficult to draw general conclusions. It would be interesting to further investigate this aspect in future studies. Women did not differ in their level of qualifications or employment statuses. The majority of women in all groups had a degree and were employed, although numerically the percentages were lower in the NPE group. Women also did not differ in their full scale IQ as predicted by the WTAR.

Taken together, this indicates that the women who developed postpartum psychosis in our sample were well matched in terms of common socioeconomic characteristics previously associated with this illness. Next, we investigated whether our participants share medical and obstetric characteristics that have been found to put women at risk of developing postpartum psychosis.

3.4.3 Medication

There was no difference between groups on the use of over-the-counter medication. The NPE and PE groups also did not significantly differ in the number of women taking prescribed medication at the time of the MRI scan or the mean dose of antipsychotic medication in chlorpromazine equivalents. However, women in the NPE group had a longer duration in days of exposure compared to the PE group, which concurs with the finding that women in the NPE group reported more previous episodes and had an earlier illness onset.

Although lithium has been suggested as first choice treatment for postpartum psychosis (Doucet et al., 2011; Roy & Payne, 2009), only one woman was receiving it at the time of the MRI scan. In line with previous studies, treatment of women in our study involved antipsychotics and benzodiazepines (L. S. Cohen et al., 1995; Roy & Payne, 2009; Sit et al., 2006; M.G. Spinelli, 2009). Unfortunately, it was not possible to collect the exact data concerning the length and dose of medication use

for all participants in order to calculate chlorpromazine equivalence scores. None of the women had received ECT.

3.4.4 Medical and obstetric history

Problems in pregnancy have not typically been connected to a higher risk of postpartum psychosis (V. Bergink et al., 2011; Blackmore et al., 2006; Kendell et al., 1987; Kendell, Rennie, et al., 1981; Kendell et al., 1976; Paffenbarger, 1961; Rehman et al., 1990; Valdimarsdóttir et al., 2009; Videbech & Gouliaev, 1995). However, some studies (Nager et al., 2008) suggest that women with postpartum psychosis experience more problems during pregnancy or delivery (e.g. infection from a caesarean section) or during breastfeeding (e.g. not latching on). In line with the latter study, we found a trend showing that women at risk of postpartum psychosis had experienced more problems during their most recent pregnancy, although this trend was mainly driven by the NPE group. However, there was no difference in the number of previous pregnancies that did not result in a live birth. Across all groups, the majority of women had had a previous miscarriage or termination. Fewer women in the PE group breastfed their child compared to healthy controls. This could also be as a result of the episode of severe illness after their recent delivery, making the women in the PE group too unwell or unwilling to breastfeed; it could also possibly be due to a higher use of medication.

There was no significant difference in maternal parity across groups. This differs to previous results which highlighted that primiparity is associated with a higher risk of developing postpartum psychosis (P. Agrawal et al., 1990; V. Bergink et al., 2011; Blackmore et al., 2006; Cheetham et al., 1981; Kendell et al., 1987; Kendell, Rennie, et al., 1981; Kirpinar et al., 1999; Kisa et al., 2007; Meltzer & Kumar, 1985; Paffenbarger, 1961; Paffenbarger & McCabe, 1966; Protheroe, 1969; Schöpf et al., 1984; Videbech & Gouliaev, 1995). Yet, since the sample size in our study is small, this may not be a representative finding for the population.

As reported previously, age of onset of menarche was not associated with postpartum psychosis (Paffenbarger, 1961). Groups were also matched according to the number of weeks after delivery and, by the time of the MRI scan, a similar number of women in each of the groups had already had their first period following their most recent

delivery. To conclude, women in our study did not differ in terms of their medical or obstetric history. Nonetheless, since this is not a large epidemiological sample, future studies have to further investigate a potential link between postpartum psychosis and medical and obstetric characteristics. Another important aspect of mental illness is the potential use of legal or illicit drugs.

3.4.5 Nicotine, caffeine, cannabis, alcohol and other drugs of abuse

There were no group differences in coffee, tea or alcohol consumption at the time of the MRI scan. Groups also did not differ in smoking history or current smoking, although women in the NPE group had previously smoked more cigarettes than women in the PE or healthy control groups. These findings are in line with previous results showing no association between postpartum psychosis and smoking (Valdimarsdóttir et al., 2009). There are no studies investigating the use of cannabis in postpartum psychosis. Still, it has been found that people diagnosed with bipolar disorder are more prone to using cannabis than healthy controls (A. Agrawal, Nurnberger, & Lynskey, 2011). In our study, women in both the NPE and PE groups had smoked cannabis more frequently during the period of highest use and used more cannabis on average during each use compared to healthy controls. However, more women in the NPE group had previously smoked cannabis than women in the PE group. Similarly to cannabis use, there are no studies on alcohol and substance abuse in postpartum psychosis. Nonetheless, bipolar disorder has been strongly linked to a higher risk of alcohol and substance abuse (Krishnan, 2005). None of the healthy controls, but one-third of the women in both the NPE and PE groups had a history of alcohol or substance abuse. Taken together, these results suggest that there is an association between illicit drug use and mental illness, as defined in our study, but not specifically for postpartum psychosis.

3.4.6 Clinical assessments

More women in the NPE and PE groups had experienced stressful life events during the previous six months and intrusive life events during their life-time compared to healthy controls. This suggests that in the PE group stress may be an important trigger of a postpartum psychotic episode. However, since the NPE group showed

similar rates of stressful and intrusive life events, the specific association with postpartum psychosis has to be established by future studies. The groups did not differ in the number of family arrangements, but women in the NPE and PE groups had experienced more physical and sexual abuse than the healthy controls. This is in line with the finding that postpartum psychosis is not specifically associated with a problematic childhood (Bratfos & Haug, 1966; Valdimarsdóttir et al., 2009). However, bipolar disorder or psychoses unrelated to childbirth have been associated with childhood trauma (J. Savitz et al., 2009; Schäfer & Fisher, 2011). Therefore, the abuse reported in this study may be more generally linked to the development of mental illness in the women in our study. Since the sample size in these sub-analyses is very small it is difficult to generalise these findings.

Taken together, these findings support, to some extent, the view that acute stressful life events do not specifically contribute to postpartum psychosis (Brockington et al., 1990; R. Kumar et al., 1993; McNeil, 1988b; Paffenbarger & McCabe, 1966; Protheroe, 1969). Nevertheless, consistent with a large body of literature (J. Savitz et al., 2009; Schäfer & Fisher, 2011), having experienced acute stressful life events seems to be associated with a higher risk of developing mental illness, including the development of episodes of postpartum psychosis. The preliminary findings of higher rates of severe childhood trauma are also interesting considering the lack of evidence in this area in relation to postpartum psychosis; the topic deserves further investigation using larger sample sizes.

Women in the NPE group had a higher number of first-degree relatives who were diagnosed with a psychiatric illness compared to the PE group and healthy controls, which differs from previous findings which suggest a similar familial risk in postpartum psychosis and bipolar disorder unrelated to childbirth (P. Agrawal et al., 1990; Benvenuti et al., 1992; Dean et al., 1989; Kirpinar et al., 1999; Platz & Kendell, 1988; Protheroe, 1969).

Women in the NPE and PE groups scored lower on scales assessing general, current and past year functioning when compared to healthy controls and, not surprisingly, higher on mood, positive, and negative symptoms, as well as on perceived stress and anxiety scales at the time of the MRI scan. The NPE and PE groups did not significantly differ from each other on any scales, although most women in the PE group had experienced a recent episode of postpartum psychosis. These findings

seem to have two implications. Firstly, the scores of women on the mood as well as positive and negative symptom scales were quite low, indicating that all the women were relatively well by the time of the MRI scan. Secondly, women with non-postpartum episodes showed higher mood, anxiety and stress scores compared to healthy controls, although they had not suffered a recent episode. This suggests that, if validated in larger sample sizes, women with a psychiatric diagnosis may also need additional support within the first year after childbirth independently of the development of an acute mood or psychotic episode.

3.4.7 Representativeness of the “at risk” group and healthy controls

In order to assess whether women in the “at risk” group, recruited into this study, were representative of the patient population under the care of the perinatal services of the South London and Maudsley NHS Foundation Trust, we compared sociodemographic characteristics of our population with those that were available from two other studies conducted with in-patients at the Mother and Baby Unit at the Bethlem Royal Hospital (Kenny, Conroy, Pariante, Seneviratne, & Pawlby, 2013; R. Kumar et al., 1995). Kumar and colleagues (1995) reported a mean age of 29 years of women admitted to the Bethlem mother and baby unit with an affective psychosis diagnosed following childbirth. In a newer study conducted by Kenny and colleagues (2013), a mean age of 31 years was reported for new mothers that had been admitted to mother and baby unit. In comparison to these studies, the mean age of our “at risk” group was very similar, being 32 years.

In both previous studies, approximately 80% of women were either married or cohabiting, showing that this rate is also comparable to what we have found in our sample, where 75% of our women were either married or cohabiting. Approximately 60% of women were Caucasian in the studies conducted by Kumar and Kenny. Here, our sample had a slightly lower proportion with 52% of women being Caucasian in the “at risk” group. The proportion of primiparous women was similar in our study (i.e. 56%) to the women with affective psychosis in the study of Kumar (i.e. 57%), while in Kenny’s study a lower proportion of only 42% of women being primiparous was reported. Finally, of the women who took part in the study of Kumar, 50% were

employed in comparison to 60% in our study. No information was given on employment in the study of Kenny et al. (2013).

The “at risk” group matches previous reports of in-patients of the mother and baby unit on important characteristics including age, marital status, primiparity, ethnicity, and employment rate. Unfortunately, there were no further data available from these studies on type of employment or IQ, which would have allowed a more detailed comparison. However, based on these sociodemographic characteristics, it can be concluded that our “at risk” group was a representative sample of women at risk of postpartum psychosis who have taken part in previous research.

In order to match the healthy controls recruited for this study on socioeconomic background, women were recruited in the same hospital and the population as a whole was recruited from the same, relatively deprived, area in London. The results of this chapter suggest that women were well matched regarding their socioeconomic background, medical and obstetric history, especially given that there were no significant differences even without using multiple comparisons correction in this exploratory chapter. However, although there were no statistically significant differences reported in the current chapter between the “at risk” group and healthy controls, healthy controls still had numerically a higher IQ, a higher employment rate and a higher rate of women had a degree or diploma. There was also a tendency of healthy controls to have a higher age than the “at risk” group. As discussed in the paragraph 3.4.2 Sociodemographic background, this may simply reflect a greater willingness of more mature healthy mothers to take part in research compared to younger and maybe less experienced mothers. Also, differences in these factors (employment, IQ, education) are most commonly reported in case-control studies of affective and non-affective psychosis, and it has been argued that attempting to match for characteristics that may actually be a corollary of the disorder itself may add other, unknown, biases. Nevertheless, these differences are important to consider in order to interpret the results and to exclude the possibility that significant differences in the experimental paradigms are due to high functioning controls. This limitation of the study will be further discussed in chapter 7. General discussion, 7.5 Limitations, 7.5.2 Healthy controls.

3.4.8 Summary

In this exploratory chapter, women with non-postpartum episodes and women with postpartum episodes were well matched regarding their socioeconomic background, medical and obstetric history and medication use in the current study. There was no specific association between postpartum psychosis and life events, previous alcohol or illicit drug use or family history. However, there was a general association between these variables and both “at risk” groups, in line with existing evidence that they are important contributors to the development of mood and psychotic disorders.

Both “at risk” groups showed similar scores on scales assessing general functioning, mood, positive and negative symptoms, anxiety, and stress. These results indicate that women in the PE group were relatively well at the time of the MRI scan, although clinical scores suggest that both groups may need additional support within the first year after childbirth. Finally, these results suggest that women with postpartum psychosis show a similar clinical profile compared to women with non-postpartum episodes.

4. Chapter: Verbal memory

In this chapter, an overview of the relevant literature on verbal memory will be presented. Then, the logical memory paradigm of the WMS-III and a recognition paradigm, including the development and validation of the paradigm, will be described. This will be followed by the presentation of the results and their discussion with regard to the existing literature.

4.1 Introduction

As stated in the main introduction, while there are no studies assessing verbal memory in postpartum psychosis, verbal memory impairment seems to be one of the key deficits in bipolar disorder and in psychoses unrelated to childbirth (Aleman, Hijman, de Haan, & Kahn, 1999; Arts et al., 2008; Libby et al., 2012; Reichenberg, 2010; Reichenberg et al., 2009; L. J. Robinson et al., 2006). Deficits have been found in standardised cognitive test batteries assessing verbal memory, such as story recall of the WMS-III as well as in recognition tasks assessed with remember-know paradigms (Glahn et al., 2007; Libby et al., 2012; L. J. Robinson et al., 2006; Tulving, 1985; Wechsler, 1997; Wood et al., 2007).

4.1.1 *Standardised tests of verbal memory*

Conducting a meta-analysis, Robinson and colleagues (2006) showed that an impairment in immediate and delayed verbal memory is present in bipolar patients even after long symptom free periods (I.N. Ferrier et al., 1999; Kieseppa et al., 2005; L. J. Robinson & Ferrier, 2006; L. J. Robinson et al., 2006). This impairment seems to be independent of the patient's current clinical symptom profile and severity (i.e. manic, hypomanic, depressed or euthymic) (Martínez-Arán et al., 2004). However, verbal memory performance has been found to be more impaired in bipolar patients with any or a mix of the following: a history of psychosis, a longer illness, a higher number of manic episodes, frequent hospitalisations, suicide attempts (Bora et al., 2007; Martinez-Aran et al., 2008; Martínez-Arán et al., 2004; L. J. Robinson & Ferrier, 2006; J. Savitz et al., 2009). The impairment also appears to be more pronounced in the bipolar I than in the bipolar II type disorder (Martínez-Arán et al.,

2004; J. B. Savitz et al., 2008). Verbal memory deficits in bipolar disorder have also been found to remain when alcohol abuse, childhood trauma or medication effects were taken into account in the analyses (Bora et al., 2007; Martinez-Aran et al., 2008; J. B. Savitz et al., 2008). In fact, it has been suggested that the effects of medication (predominantly mood stabilisers) are small as medication free euthymic bipolar patients perform at a similar level in verbal memory tasks when compared to medicated bipolar patients (Goswami et al., 2009).

Verbal memory dysfunction has also been demonstrated in patients suffering from psychoses unrelated to childbirth (Wood et al., 2007). Deficits have been consistently reported in schizophrenia in immediate and delayed recall (Reichenberg, 2010). Dysfunction has been found to be present already at the time of illness onset and even before onset in high risk individuals (Brewer et al., 2006; R.E. Carrión et al., 2011; Wood et al., 2007). This is different to findings on bipolar disorder, as the deficit seems to be independent of chronicity (i.e. non-progressive) (Brewer et al., 2006; R.E. Carrión et al., 2011; Wood et al., 2007). In fact, a stable association between verbal memory impairment and psychoses unrelated to childbirth has been suggested; it seems to be little influenced by age, medication use, duration of illness, severity of psychopathology or positive symptoms (Aleman et al., 1999; Reichenberg, 2010). However, another study has reported an association between of length illness and other forms of memory (Pelletier, Achim, Montoya, Lal, & Lepage, 2005). An association with negative symptoms has been reported repeatedly (Aleman et al., 1999; Reichenberg, 2010). In addition, verbal memory impairment has been found to negatively correlate with emotional discomfort (Lysaker, Bell, Greig, & Bryson, 2000). Deficits have also been confirmed using a different assessment of verbal memory, in the form of remember-know paradigms.

4.1.2 Remember-know paradigms

It has been proposed that recognition is supported by two independent processes: “recollection” and “familiarity” (Jacoby, 1991; Mandler, 1980; Rajaram & Roediger, 1997; Yonelinas, 1999, 2001, 2002). Recollection and familiarity can be assessed with remember-know paradigms, which were first introduced by Tulving (1985) in order to assess retrieval that is accompanied by conscious experiences (Tulving,

1985). Although it was first used to explore the difference between episodic and semantic memory (Tulving, 1985), the remember-know paradigm is now widely used to investigate recollection and familiarity. Recollection and familiarity can be thought of as the memory processes and “remember” and “know” responses as the test format (Migo, Mayes, & Montaldi, 2012). This procedure is the most commonly used method to investigate dual process theories of recognition memory (Migo et al., 2012). Specifically, during these paradigms participants indicate that they either remember or know a previously presented test-stimulus (e.g. words). With a remember judgement, a participant indicates that the stimulus evokes recollection of a specific episode in which it was presented previously (e.g. memory for spatiotemporal context). With a know judgement, a participant indicates that the stimulus does not evoke the recollection of a specific episode but instead a sense of familiarity (no retrieval of contextual information; for example recognising a face, but not remembering to whom it belongs) (R. N. A. Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Tulving, 1985). It has been suggested that different neural substrates underlie remember and know judgements (R. N. A. Henson et al., 1999; Libby et al., 2012; Yonelinas, 2002). In particular, recollection is said to be supported within the medial temporal lobe by the hippocampus, while familiarity is not associated with hippocampal involvement but rather by the perirhinal and prefrontal cortices (Aly, Yonelinas, Kishiyama, & Knight, 2011; Eichenbaum, Yonelinas, & Ranganath, 2007; R. Henson, 2005; R. N. A. Henson et al., 1999; Libby et al., 2012; Yonelinas, 2002). However, not all studies have found a functional division (R. Henson, 2005).

While there appears to be a paucity of research investigating remember-know paradigms in bipolar disorder, there is plenty of research into this area in regards to psychoses unrelated to childbirth. Some studies report an overall deficit in recognition (Pelletier et al., 2005; van Erp et al., 2008), although commonly a deficit in recollection performance is reported in these patients, while familiarity seems to be intact (Brébion, Gorman, Malaspina, Sharif, & Amador, 2001; Huron et al., 1995; Martin et al., 2011; Thoma, Zoppelt, Wiebel, & Daum, 2006; van Erp et al., 2008). The recollection deficit has been further associated with severity of depressive and negative symptoms, length of illness, as well as slowing of processing speed, but not with positive psychotic symptoms (Brébion et al., 2001; Pelletier et al., 2005; Thoma et al., 2006). It has been speculated that a recollection deficit might be caused by

differences in encoding between patients and healthy controls and also by an increase in the false alarm rates (Brébion et al., 2001; Thoma et al., 2006). Some studies also report an impairment in familiarity (Caza, Doré, Gingras, & Rouleau, 2011; A. P. Weiss, Goff, Duff, Roffman, & Schacter, 2008). Moreover, in a recent quantitative review a more consistent deficit in familiarity was revealed, although still less pronounced than in recollection (Libby et al., 2012).

In summary, verbal memory dysfunction has consistently been found in bipolar disorder and psychoses unrelated to childbirth independently of the task employed. Therefore, we expected that women at risk of postpartum psychosis would show, in comparison to healthy controls, impaired verbal memory performance. Furthermore, we proposed that impairments in verbal memory would be more pronounced in women who had developed postpartum psychosis episodes, compared to women who had not developed postpartum psychotic episodes, and to healthy controls. These hypotheses belong to the group of secondary hypotheses of this thesis. In order to test these hypotheses, the two most commonly used verbal memory tasks will be used. A standardised verbal memory test (i.e. the logical memory I and II of the Wechsler Memory Scale-III) and the remember-know paradigm.

4.2 Methods

4.2.1 Participants, design, analyses and procedures

Methods are described in chapter 2. For information on the combined group analyses and sub group analyses please see chapter 2 and chapter 3.

4.2.2 Tasks

4.2.2.1 Logical memory I and II

In order to assess immediate and delayed verbal memory performance, logical memory I and II of the WMS-III were carried out according to a standardised procedure (Wechsler, 1997). For the immediate memory (logical memory I), two stories were orally presented. The second story was presented twice. The participants were asked to retell the stories from memory. For the delayed logical memory test

(logical memory II), participants were asked to retell both stories from the immediate condition after a 25-30 minute delay.

4.2.2.2 *Remember-know paradigm*

In order to assess immediate and delayed verbal memory performance in terms of recognition, participants completed a remember-know paradigm, consisting of two stages: encoding and retrieval. In the following section the development and validation of the task will be discussed.

4.2.2.2.1 Development and validation of the remember-know paradigm

A new verbal memory task was designed for this study based on previous tasks used (Craig et al., 2008; Craig et al., 2007). Three word lists (three encoding and three retrieval playlists) were developed and tested in a pilot. Words were chosen out of the British National Corpus (BNC) word collection (<http://ucrel.lancs.ac.uk/bncfreq/>). Nouns (2578 in total) were chosen based on the Medical Research Council Psycholinguistic Database (Wilson, 1988) (<http://www.psych.rl.ac.uk>) according to the following inclusion criteria:

- 1) Frequency between 10 and 100 (per million words).
- 2) Words with more than four and less than eight letters.
- 3) Concreteness above 400.

Subsequently, words lists were categorised into natural and “man made”, leaving two word lists with 255 words (man made) and 234 words (natural). Out of these two lists, three encoding playlists, each with 35 natural and 35 man made words, were created (words were randomly selected). For each encoding playlist (encoding 1, 2, 3) a matching retrieval playlist was created (retrieval 1, 2, 3), each consisting of 70 “old” (i.e. previously presented) and 35 “new” (i.e. not previously presented) words (17 natural and 18 man made words).

Using the MRC Psycholinguistic Database, word lists were matched according to:

1. Frequency.
2. Concreteness (Range 400-700).
3. Imageability (Range 400-700).
4. Number of letters (length).
5. Number of syllables.

Word lists were analysed and compared using one-way ANOVA within SPSS 20. Following the matching of the playlists, nine healthy volunteers (male and female and aged similarly to participants) were tested on each playlist in order to test if they were matched in terms of performance using repeated measures ANOVA. For simplicity of the task validation we checked only for overall recognition performance, adjusting for any floor and ceiling effects systematically (Snodgrass & Corwin, 1988).

Variables of interest for validation of the encoding playlists included:

- 1) Reaction time (RT).
- 2) Percentage of correctly identified words.

Variables of interest for the validation of the retrieval playlists included:

- 1) RT.
- 2) Hit rate = $\frac{\text{hits}+0.5}{\text{old items}+1}$
- 3) False alarm rate = $\frac{\text{false alarms}+0.5}{\text{new items}+1}$
- 4) Overall sensitivity (recognition) $d' = z \text{ score (hit rate)} - z \text{ score (false alarm rate)}$.

No significant differences between playlists were found on 1) frequency 2) concreteness 3) imageability 4) number of letters (length) and 5) number of syllables (see Table 4.1).

Table 4.1 Word lists verbal memory task

Encoding (N=70)	List 1	List 2	List 3	F(2, 207)	p
Frequency	31.10(20)	33.96(22)	33.24(23)	0.31	0.73
Concreteness	585.3(25)	581.74(38)	581.53(30)	0.31	0.74
Imageability	584.04(33)	581.19(33)	581.73(35)	0.14	0.87
Length	5.01(1)	5.26(1)	5.14(1)	0.88	0.42
Syllables	1.47(.58)	1.51(.65)	1.41(.58)	0.51	0.61
Retrieval (N=105)	List 1	List 2	List 3	F(2, 312)	p
Frequency	32.81(20)	31.86(22)	31.42(23)	0.11	0.89
Concreteness	585.62(27)	583.01(35)	585.45(30)	0.26	0.79
Imageability	583.12(34)	579.89(36)	581.41(34)	0.62	0.54
Length	5.05(1)	5.20(1)	5.12(1)	0.49	0.61
Syllables	1.44(.55)	1.50(.66)	1.45(.58)	0.37	0.69

Table 4.1 shows the mean values of the variables (standard deviation in brackets), the F-value (degrees of freedom) and corresponding p-value.

Further, no significant differences between the playlists were found based on the behavioural performance of participants. Also, the retrieval playlists significantly correlated with each other (smallest $r(9)=.66$, largest $p=.05$), validating the similarity of the playlists (see Table 4.2).

Table 4.2 Performance results word lists verbal memory task

Encoding (N=9)	List 1	List 2	List 3	F(2, 7)	p
RT	1415(151)	1409(145)	1388(184)	0.06	0.94
Percentage of correct words	93.49(3)	94.29(2)	93.96(3)	0.68	0.54
Retrieval (N=9)	List 1	List 2	List 3	F(2, 7)	p
RT	1328(237)	1362(179)	1340(228)	0.15	0.86
Hit rate	0.89(0.06)	0.87(0.09)	0.85(0.11)	1.44	0.29
False alarm rate	0.08(0.11)	0.06(0.06)	0.06(0.05)	0.23	0.80
d'	3.01(0.98)	2.91(0.61)	2.88(0.85)	0.25	0.78

Table 4.2 shows the mean values of participants' responses (standard deviation in brackets).

RT=reaction times (shown in milliseconds). Also shown are the F-value (degrees of freedom) and corresponding p-value. d' sensitivity index.

4.2.2.2.2 Procedure

During encoding, a sequence of words was presented on a computer screen to the participants, who had to decide whether the words presented to them represented natural (e.g. tree) or man made (e.g. house) objects by pressing "1" or "0" on the keyboard, respectively (see Figure 4.1). The encoding task included 70 words (35

natural and 35 man made objects) presented to participants for 3.5 seconds each (independent of participants' responses).

Figure 4.1 Encoding part of the verbal memory task

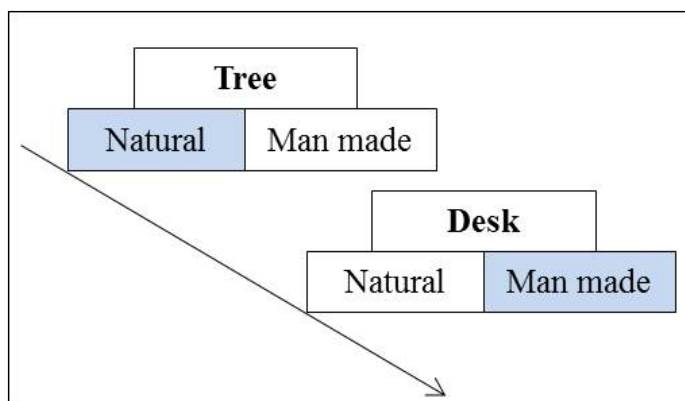


Figure 4.1 shows the encoding part of the verbal memory task. Participants had to decide whether a word was natural or man made by pressing either the 1 or 0 on a keyboard, respectively.

Recognition took place after a period of 90 minutes; after this time participants were shown a stream of words again and had to decide whether the words presented were old words (i.e. presented in the previous playlist). In order to assess recollection and familiarity, participants had to decide whether they remembered – (R) the item (i.e. whether they recollected that actual presentation of the word in the playlist and linked it with any context) or whether they just “knew – (K)” that the item was old (i.e. whether the item seemed familiar to them but they did not recall any associated details from the prior exposure) by pressing 9 or 0 on the keyboard, respectively. New words (i.e. not previously presented in the encoding playlist) had to be identified by pressing 1 on the keyboard (see Figure 4.2).

Figure 4.2 Retrieval part of the verbal memory task

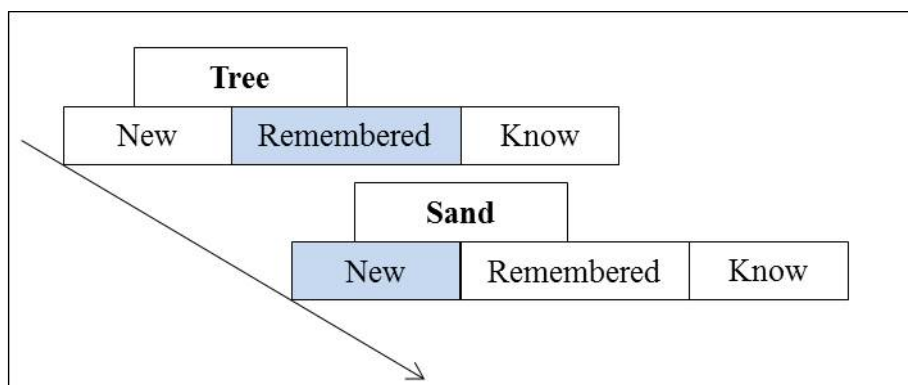


Figure 4.2 shows the retrieval part of the verbal memory task. Participants had to decide whether they remembered, knew or did not recognise a word by pressing 9, 0 or 1 on the keyboard, respectively.

The recognition task consisted of 105 words (70 old words and 35 new words). Length of presentation was determined by participants' reaction time. The possible response options of the task are shown in Table 4.3. Instructions were given verbally shortly before the encoding and retrieval part and were based on Rajaram (1993) (Rajaram, 1993). Then, it was confirmed that participants had understood and followed the instructions by giving them a test trial (Migo et al., 2012).

Table 4.3 Response outcomes

		Response options		
		<i>old (remembered)</i>	<i>old (know)</i>	<i>new</i>
Word	<i>old</i>	hit (R)	hit (K)	miss
	<i>new</i>	false alarm (R)	false alarm (K)	correct rejection

Table 4.3 shows the response options for the retrieval part of the verbal memory task. Participants could decide whether a word was previously presented (i.e. remember or know) or whether it was new.

4.2.3 Analyses

4.2.3.1 Logical memory

The raw score scale of logical memory I ranges from 0 to 75 points and for logical memory II from 0 to 50 points. Scores were converted using age adjusted standard scores of the WMS-III, which range from 1 to 19, with 10 representing the population average and with every three point increment or decrement representing one standard deviation (Wechsler, 1997). Variables of interest were logical memory I and II standard scale scores.

4.2.3.2 Remember-know paradigm

For the encoding, the following variables of interest were calculated:

- 1) RT.
- 2) Percentage of correctly identified words.

For the recognition analysis, the hit rate and the false alarm rate were calculated separately for recollection and familiarity according to the statistical independence assumption (Yonelinas, 1999, 2001, 2002). This most widely used method for the calculation assumes that the familiarity reported in a know response is the same as the familiarity that can accompany a remember response in terms of accuracy and frequency (Migo et al., 2012). Again, hit and false alarm rates were systematically corrected for ceiling and floor effects (Snodgrass & Corwin, 1988).

In the following section the calculation of variables is presented by equations:

The remember hit rate was calculated by

$$\text{Hit rate}(\text{remember}) = \frac{\text{hits (R)} + 0.5}{\text{old items} + 1}$$

The remember false alarm rate was calculated by

$$\text{False alarm rate (remember)} = \frac{\text{false alarms (R)} + 0.5}{\text{new items} + 1}$$

The know hit rate was calculated by

$$\text{Hit rate}(\text{know}) = \frac{\text{hits (K)} + 0.5}{(\text{old items} + 1) - \text{hits (R)}}$$

The know false alarm rate was calculated by

$$\text{False alarm rate (know)} = \frac{\text{false alarms (K)} + 0.5}{(\text{new items} + 1) - \text{false alarms (R)}}$$

In order to provide sensitivity measures (i.e. ability to discriminate signal from noise) of participants, the sensitivity index d' was calculated. The higher the score of d' , the higher the sensitivity, with typical values below 4 and around 2 (Stanislaw & Todorov, 1999).

The remember d' was calculated by

$$d' (R) = Z (\text{hit rate } (R)) - Z (\text{FA rate } (R))$$

The know d' was calculated by

$$d' (K) = Z (\text{hit rate } (K)) - Z (\text{FA rate } (K))$$

In addition, we reported the remember and know response biases, indicating the position of the participants' decision criterion with respect to the neutral point $c=0$, where there is no response bias (Stanislaw & Todorov, 1999). Values are ranging from -1 to +1. Values less than 0 indicate a bias towards the “yes” response (i.e. here a “remember “or know response) and values greater than 0 indicate a bias toward the “no” response (i.e. here a new response).

The remember response bias was calculated by

$$c (R) = - \frac{Z (\text{hit rate } (R)) + Z (\text{FA rate } (R))}{2}$$

The know response bias was calculated by

$$c (K) = - \frac{Z (\text{hit rate } (K)) + Z (\text{FA rate } (K))}{2}$$

In summary, variables of interest were:

- 1) Overall recognition.
- 2) Remember performance as indicated by $d' (R)$.
- 3) Know performance as indicated by $d' (K)$.
- 4) Response bias for the remember performance as indicated by $c (R)$.
- 5) Response bias for the know performance as indicated by $c (K)$.
- 6) RT.

Group was the between subjects factor and memory performance as indicated by d' (R) versus d' (K) and response bias as indicated by c (R) versus c (K) the within-subjects factors.

4.3 Results

4.3.1 Logical memory I and II

Due to a problem with the recording of the task, only the data of 33 women could be analysed (NPE=10, PE=9, healthy controls=14).

4.3.1.1 Combined group analysis (CGA)

In the following section the “at risk” group as a whole will be compared to healthy controls. As shown in Figure 4.3, there was a significant difference between the “at risk” group and healthy controls on the immediate memory performance ($t(31)=2.19$, $p=.04$), with the “at risk” group performing worse than the healthy controls. There was, however, no significant group difference for the delayed memory performance ($t(31)=1.59$, $p=.12$); see Figure 4.4 and for scores see Table 4.4.

Figure 4.3 Logical memory I (CGA)

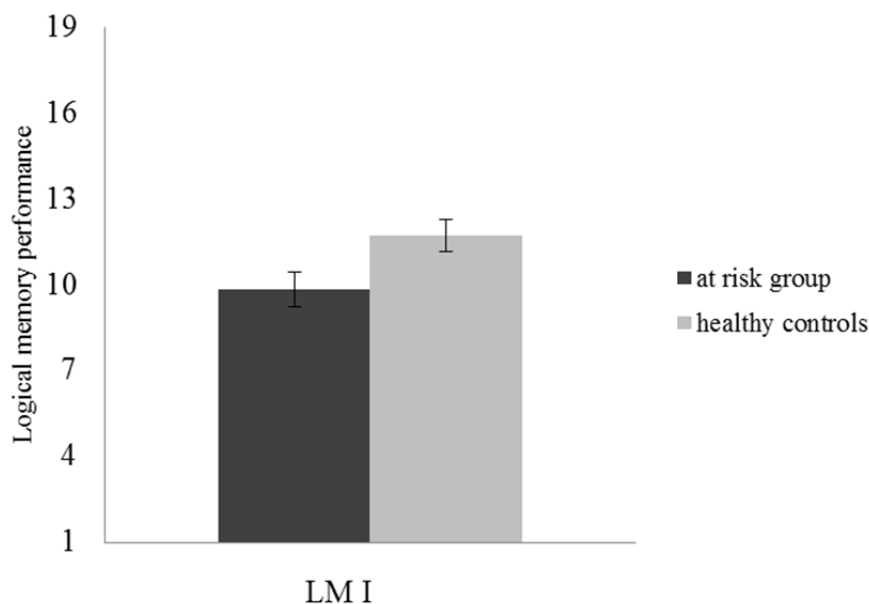


Figure 4.3 shows the mean performance of the “at risk” group and healthy controls on immediate memory (LM I). The error bars show the standard error of mean (SEM).

Figure 4.4 Logical memory II (CGA)

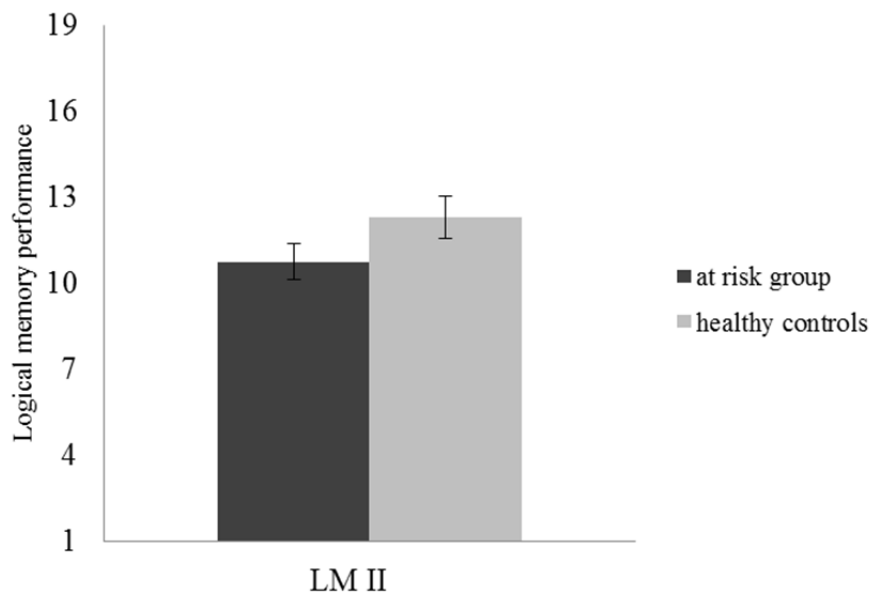


Figure 4.4 shows the mean performance of the “at risk” group and healthy controls on delayed memory (LM II). The y-axis shows the mean performance. The error bars show the standard error of mean (SEM).

Table 4.4 Logical memory scores (CGA)

Groups	“at risk” M (SD)	healthy controls M (SD)
LM I standard scores	9.82 (2.65)	11.71 (2.05)
LM I raw scores	39.68 (10.26)	46.14 (8.10)
LM II standard scores	10.74 (2.75)	12.29 (2.81)
LM II raw scores	26.00 (7.88)	30.14 (8.05)

Table 4.4 shows the raw and standard scores of the “at risk” group and healthy controls on immediate (LM I) and delayed (LM II) memory. M=mean. SD=standard deviation.

4.3.1.2 Sub group analysis (SGA)

As shown in Figures 4.5 and 4.6, there were no significant differences between the NPE, PE and healthy controls on the immediate or delayed memory performance ($F(2,29)=2.139$, $p=.11$; $F(2,29)=1.81$, $p=.18$); for scores see Table 4.5.

Figure 4.5 Logical memory I (SGA)

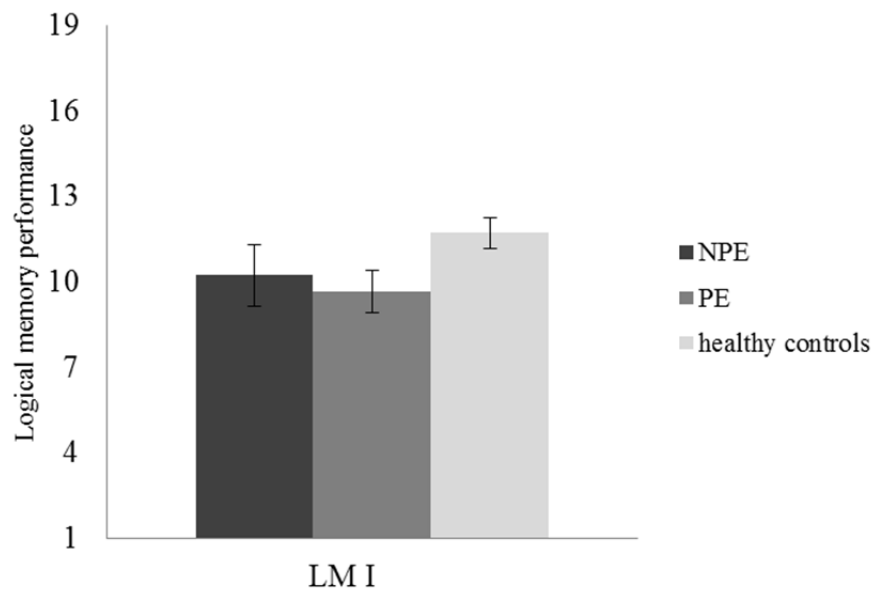


Figure 4.5 shows the mean performance of the NPE, PE and healthy control groups on immediate (LM I) memory. The y-axis shows the mean performance. The error bars show the standard error of mean (SEM).

Figure 4.6 Logical memory II (SGA)

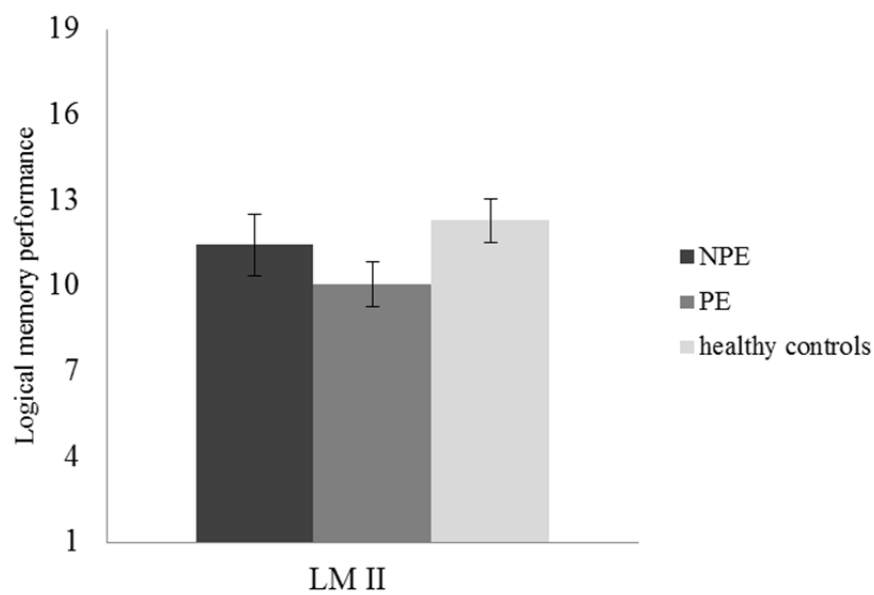


Figure 4.6 shows the mean performance of the NPE, PE and healthy control groups on delayed (LM II) memory. The y-axis shows the mean performance. The error bars show the standard error of mean (SEM).

Table 4.5 Logical memory scores (SGA)

Groups	NPE M (SD)	PE M (SD)	healthy controls M (SD)
LM I standard scores	10.22 (3.19)	9.67 (2.24)	11.71 (.59)
LM I raw scores	41.33 (12.14)	39.00 (8.75)	46.14 (8.10)
LM II standard scores	11.44 (3.21)	10.00 (2.35)	12.29 (2.81)
LM II raw scores	28.00 (9.21)	23.89 (6.74)	30.14 (8.05)

Table 4.5 shows the raw and standard scores of the NPE, PE and healthy control groups on immediate (LM I) and delayed (LM II) memory. M=mean. SD=standard deviation.

4.3.1.3 Additional analysis

There were no significant correlations between the HAM-D, PANSS, or length of illness and logical memory performance (largest $r(19)=.39$, smallest $p=.14$). There were also no significant effects of antipsychotic medication or having had a menstrual period after delivery when the two variables were included into the model as fixed factors (yes/no) (smallest $p=.23$).

As a further additional analysis we compared all women who were at risk of postpartum psychosis due to a diagnosis of bipolar disorder ($N=11$) or other diagnoses (i.e. schizoaffective disorder, postpartum psychosis or family history) ($N=8$) and healthy controls ($N=14$). However, there were no significant differences between groups in either the immediate ($F(2,30)=2.44$, $p=.10$) or delayed recall ($F(2,30)=1.27$, $p=.30$).

4.3.2 Remember-know paradigm

Three women could not complete the verbal memory task due to time reasons (i.e. the gap between encoding and retrieval was too long due to a delay in the MRI scan), leaving a total of 43 women for analysis (NPE=12, PE=11, and healthy controls=20). One healthy control was excluded for floor performance suggesting no engagement with the task.

4.3.2.1 Encoding

There were no significant differences between groups in the percentage of words correctly identified as natural or man made or RT (smallest $p=.26$). In each group the percentage of correctly identified words was above 89%. The mean RT for each group was between 1154ms and 1287ms.

4.3.2.2 Combined group analysis (CGA)

In the following section the “at risk” group will be compared to healthy controls. As shown in Figure 4.7, a repeated measures ANOVA showed no interaction effect between group (“at risk” versus healthy controls) and memory performance as indexed by d' (remember versus know) ($F(1,40)=.82$, $p=.37$). However, there was a significant main effect of group with the “at risk” group having a lower overall memory performance than healthy controls ($F(1,40)=5.72$, $p=.02$). This effect remained significant when we excluded the women that could not be analysed for the logical memory task ($F(1,30)=4.88$, $p=.04$). This group difference was also significant when overall recognition performance as indicated by d' was compared ($F(1,40)=9.17$, $p=.01$). There was also a significant main effect of memory performance ($F(1,40)=16.75$, $p=.01$) as both groups showed a higher remember than know performance. We also investigated the response bias. There was no interaction effect between group and response bias as indexed by c (R versus K) ($F(1, 40)=.02$, $p=.90$) and no main effects of group or response bias ($F(1, 40)=.02$, $p=.76$; $F(1, 40)=2.28$, $p=.14$, respectively). The RT did not differ between groups ($t(40)=-.05$, $p=.96$). For scores see Table 4.6.

Figure 4.7 Memory performance (CGA)

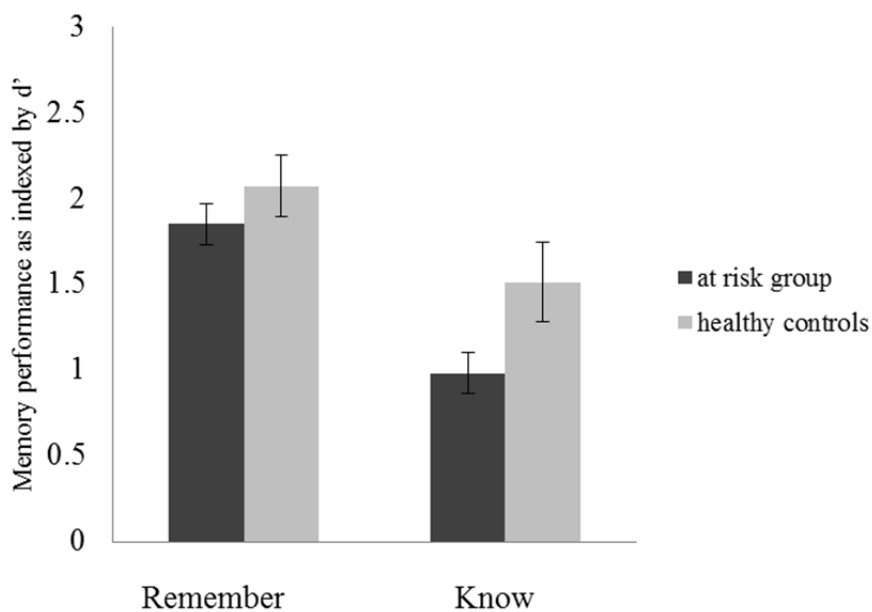


Figure 4.7 shows the mean performance of the “at risk” and healthy control groups on memory performance as indexed by d' (remember and know). The y-axis shows the mean performance. The error bars show the standard error of mean (SEM).

Table 4.6 Remember and know responses (CGA)

Groups	“at risk” M (SD)	healthy controls M (SD)
Remember		
d'	1.85 (.59)	2.07 (.81)
c	.55 (.55)	.56 (.52)
Hit rate	.63 (.24)	.65 (.24)
False alarm rate	.09 (.08)	.08 (.07)
Know		
d'	.98 (.58)	1.51 (1.02)
c	.77 (.78)	.82 (.58)
Hit rate	.42 (.26)	.48 (.28)
False alarm rate	.16 (.21)	.08 (.07)
RT	1406 (266)	1402 (193)
Overall d'	1.76 (.55)	2.39 (.81)

Table 4.6 shows the scores of the “at risk” and healthy control groups on memory performance. M=mean. SD=standard deviation.

4.3.2.3 Sub group analysis (SGA)

In the following section the NPE and PE groups will be compared to each other and healthy controls. As can be seen on the graph in Figure 4.8, a repeated measures between subjects ANOVA did not show an interaction effect between group (NPE, PE and healthy controls) and memory performance as indexed by d' (R versus K) ($F(2, 38)=1.67$, $p=.20$). There was a strong trend towards a significant main effect of group ($F(1,38)=2.91$, $p=.07$). This trend remained when we excluded the women that could not be analysed for the logical memory task ($F(2,28)=2.26$, $p=.09$). Groups differed significantly when we compared overall recognition as indicated by d' ($F(1,38)=4.41$, $p=.02$). Post-hoc t-tests with Bonferroni correction showed a significant difference between the NPE group and healthy controls ($p=.04$) and a trend between the PE group and healthy controls ($p=.07$). There was no difference between the NPE and PE group following Bonferroni correction ($p=.84$). Again, there was a significant main effect of memory performance as all groups had a better remember than know performance ($F(1,38)=18.35$, $p=.01$). We also investigated response bias. There was no significant interaction effect between group and response bias as indexed by c (R versus K) ($F(2,38)=.50$, $p=.95$). There were also no significant main effects for group or response bias ($F(2, 38)=1.05$, $p=.36$; $F(2,38)=2.27$, $p=.14$, respectively) or significant group differences in RT ($F(2,38)=.12$, $p=.88$). For scores see Table 4.7.

Figure 4.8 Memory performance (SGA)

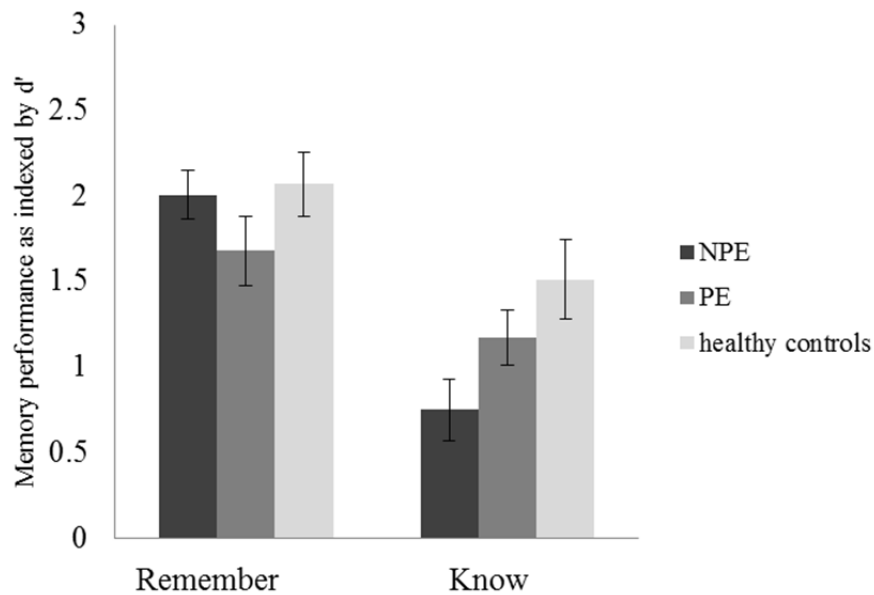


Figure 4.8 shows the mean performance of the NPE, PE and healthy control groups on memory performance as indexed by d' (remember and know). The y-axis shows the mean performance. The error bars show the standard error of mean (SEM).

Table 4.7 Remember and know responses (SGA)

Groups	NPE M (SD)	PE M (SD)	healthy controls M (SD)
Remember			
d'	2.01 (.48)	1.68 (.68)	2.07 (.81)
c	.38 (.39)	.65 (.65)	.56 (.52)
Hit rate	.71 (.15)	.57 (.30)	.66 (.25)
False alarm rate	.10 (.08)	.09 (.08)	.08 (.07)
Know			
d'	.75 (.60)	1.17 (.54)	1.51 (1.02)
c	.70 (.98)	.83 (.62)	.82 (.58)
Hit rate	.41 (.30)	.42 (.28)	.48 (.29)
False alarm rate	.21 (.29)	.12 (.11)	.08 (.07)
RT	1363 (267)	1405 (246)	1402 (193)
Overall d'	1.71 (.72)	1.79 (.39)	2.39 (.81)

Table 4.7 shows the scores of the NPE, PE and healthy control groups on memory performance. M=mean. SD=standard deviation.

4.3.2.4 Additional analysis

There were no significant correlations between age, HAM-D, PANSS, or length of illness and overall recognition (largest $r(43)=.14$, smallest $p=.38$). There were further no significant effects found of antipsychotic medication or having had a period after delivery when the two variables were taken into the model as fixed factors (yes/no) on overall recognition (smallest $p=.19$).

As a further additional analysis we compared all women who were at risk of postpartum psychosis due to a diagnosis of bipolar disorder ($N=12$) or other

diagnoses (i.e. schizoaffective disorder, postpartum psychosis or family history) (N=11) and healthy controls (N=19). There was a significant group difference ($F(2,39)=3.26, p=.05$) with the bipolar patients performing worse compared to healthy controls following pairwise comparisons with Bonferroni correction ($p=.05$). Women who were “at risk” due to other diagnoses also performed numerically worse; however, this difference was not significant following Bonferroni correction ($p=.48$). There was no difference between women diagnosed with bipolar disorder and other “at risk” women on memory performance ($P=1$).

4.4 Discussion

In this chapter, the verbal memory performance of women at risk of postpartum psychosis was investigated with the logical memory paradigm of the WMS-III assessing recall and a recognition paradigm assessing recollection and familiarity. We expected that women who are at risk of postpartum psychosis would show deficits in both paradigms compared to healthy controls. Furthermore, we proposed that women who developed postpartum psychotic episodes would perform worse than women who had non-postpartum episodes and healthy controls. The results of this chapter belong to the secondary hypotheses of this thesis and therefore, it is important to note that the tasks to assess verbal memory may be underpowered.

4.4.1 Logical Memory

As expected in our first hypothesis, women “at risk” showed an impaired verbal memory performance compared to healthy controls as shown in a worse immediate recall (Aleman et al., 1999; Arts et al., 2008; Libby et al., 2012; Reichenberg, 2010; Reichenberg et al., 2009; L. J. Robinson et al., 2006). The performance of the healthy controls was similar to previous studies in psychiatric populations (Bell, 2006; Kieseppa et al., 2005). Therefore, it is unlikely that the difference was due to a superior performance of the healthy controls. Women did not differ significantly on the delayed recall of the stories. One potential explanation for this result could be that we did not have sufficient power to detect a statistically significant delayed memory effect. Indeed, “at risk” women did still perform lower than healthy controls numerically. Contrary to our second hypothesis, there were no significant differences

between women with non-postpartum and postpartum episodes on either the immediate or delayed memory recall of the stories. Our findings show that women “at risk”, including women with non-postpartum and postpartum episodes, share common cognitive impairments in verbal memory with bipolar disorder and psychoses unrelated to childbirth (I.N. Ferrier et al., 1999; Kieseppa et al., 2005; L. J. Robinson & Ferrier, 2006; L. J. Robinson et al., 2006; Wood et al., 2007).

4.4.2 Remember-know paradigm

In line with our first hypothesis, women “at risk” showed an overall impaired memory performance on the remember-know paradigm compared to healthy controls. Somewhat surprising was the finding that the remember performance of “at risk” women was better than the know performance, given that previous reports often highlighted a more impaired recollection process in psychoses unrelated to childbirth (Brébion et al., 2001; Huron et al., 1995; Martin et al., 2011; Thoma et al., 2006; van Erp et al., 2008). However, as highlighted in a recent review, familiarity deficits have been found in psychoses unrelated to childbirth, even though they seem less strongly associated with the illness than recollection impairment (Libby et al., 2012). Furthermore, the fact that the remember scores were higher than the know scores in general fits previous results, stating that remember judgements are more common than know judgements (R. N. A. Henson et al., 1999). Not in line with our second hypothesis and similarly to the logical memory results, there were no significant differences between women with non-postpartum and postpartum episodes in terms of recollection and familiarity. Both groups differed, however, from healthy control in overall recognition performance. Again, these findings further support the idea that women with postpartum psychosis do not show a different cognitive profile to patients that have non-postpartum mood or psychotic episodes and have a similar cognitive dysfunction as seen in bipolar disorder and psychosis unrelated to childbirth (Aleman et al., 1999; Arts et al., 2008; Libby et al., 2012; Reichenberg, 2010; Reichenberg et al., 2009; L. J. Robinson et al., 2006). Differences between the “at risk” group and healthy controls were not explained by differences in encoding or in false alarm rates *per se* as previously suggested (Brébion et al., 2001; Thoma et al., 2006), as all women showed a similar performance on these variables. Also, women did not differ in their reaction time during encoding or retrieval and there

was no difference in response bias between groups, suggesting no differences in the strategic approach to the task. In general, all groups showed a positive response bias for both remember and know responses, typically indicating a conservative criterion leading to fewer false alarm rates (Stanislaw & Todorov, 1999).

4.4.3 Additional analysis

Verbal memory dysfunction was not associated with higher scores on depression or positive or negative psychotic symptoms. This is not in line with previous studies, which have reported lower verbal memory performance for patients who report more depressive or negative symptoms in bipolar disorder (Aleman et al., 1999; Brébion et al., 2001; Pelletier et al., 2005; Thoma et al., 2006). A lack of association with positive symptoms has been shown before (Lysaker et al., 2000). No association was found with length of illness (or age for the remember-know paradigm). It has been reported that chronicity is associated with verbal memory impairment in bipolar disorder and with recognition memory in schizophrenia (Pelletier et al., 2005; L. J. Robinson & Ferrier, 2006). Consequently, our finding that verbal memory performance was not related to length of illness differs to literature in bipolar disorder. Nonetheless, one important difference is that many women in our sample had just suffered one illness episode and, therefore, it may not be possible to draw valid conclusions on the basis of this single evaluation.

Antipsychotic medication did not have a significant effect on performance in either task when taken into the model as a dichotomous variable, which further supports the notion that verbal memory impairment in bipolar disorder and psychoses unrelated to childbirth is not an artefact of psychotropic medications and typically remains even once medications are taken into account (Goswami et al., 2009; L. J. Robinson et al., 2006; J. B. Savitz et al., 2008). In addition, we assessed whether there was a performance difference between women who had already recovered their regular menstrual cycle after delivery and those who had not. This was in order to find out whether there might have been an influence of oestrogens on verbal memory performance (Craig et al., 2008; Craig et al., 2007). Although having had a menstrual period did not have a direct significant effect on the results, we are aware that this is a very primary hormonal measure from which no firm conclusion can be drawn.

Unfortunately, it was not possible for us to recruit all women at exactly the same time point after delivery and some women were already using contraception. Therefore, for this sample we were unable to investigate hormonal levels with more sophisticated measures.

4.4.3.1 Impact of bipolar disorder

Women who were diagnosed with bipolar disorder did not show impaired performance compared to healthy controls on the logical memory task, but were impaired for recognition memory. Since there is a paucity of research on recognition deficits in bipolar disorder, this is one of the first studies to report an impairment. Given that women who were at risk of postpartum psychosis due to “other” diagnoses also performed numerically lower on the recognition paradigm compared to the healthy controls, as well as the apparent performance differences between women “at risk” due to bipolar disorder and women “at risk” due to “other” diagnoses on the two tasks, it is difficult to draw a firm conclusion about the influence of bipolar disorder *per se* on our results. However, based on these findings it seems reasonable to assume that women who have suffered from postpartum psychosis show similar deficits in their cognitive profile to those found in bipolar disorder.

4.4.4 Conclusion

This is the first study investigating verbal memory performance in women at risk of postpartum psychosis. As expected, we have found a significant impairment in verbal memory performance, including deficits in recall and recognition (i.e. recollection and familiarity) for women at risk of postpartum psychosis. Both groups of women (those with non-postpartum episodes and those with postpartum episodes) showed a similar impaired performance compared to healthy controls, indicating that women with postpartum psychosis show a similar cognitive profile to bipolar disorder and psychoses unrelated to childbirth. It is important to acknowledge, that if the overall multiple comparison correction is applied ($P < 0.001$) none of the results is still significant. However, the fact that this deficit emerged in two different tasks in a

relatively small sample of women suggests that this is a robust finding and should be a key area in future research.

5. Chapter: Working memory

In this chapter, an overview of the relevant fMRI literature on working memory will be presented. Then, the N-back working memory task, used in the current study, and additional details of the analysis will be described. This will be followed by the presentation of the behavioural and imaging results and their discussion in the context of the existing literature.

5.1 Introduction

Similar to other domains of cognitive functioning, no studies on working memory function have been conducted in women at risk of, or suffering from, postpartum psychosis. However, working memory dysfunction is considered one of the main impairments in bipolar disorder and psychoses unrelated to childbirth and is therefore of potential relevance to psychosis related to childbirth (Bora et al., 2010; I.N. Ferrier et al., 1999; Libby et al., 2012; Mur et al., 2007; L. J. Robinson et al., 2006; J. B. Savitz et al., 2008; Torres, Boudreau, & Yatham, 2007; Valli et al., 2012). Working memory is the ability to temporarily maintain and manipulate information for future action and is important for many complex cognitive processes (Baddeley, 2000; D.M. Barch & Ceaser, 2012). Often used for the assessment of working memory are tasks requiring storage and maintenance or maintenance and manipulation of task-relevant information (e.g. keeping a sequence of numbers in mind that is needed later on in the task) (Reichenberg, 2010).

In fMRI, the N-back task is most commonly used in order to assess working memory and was therefore chosen in this study, although its reliability and construct validity has been criticised in the past (Gevins & Cutillo, 1993; Jaeggi, Buschkuhl, Perrig, & Meier, 2010; Kirchner, 1958; Owen et al., 2005). The N-back task requires on-line monitoring, updating, and manipulation of remembered information by asking participants to remember sequences of letters. This continuous performance task is said to place great demands on working memory (Glahn et al., 2005; Owen et al., 2005). As shown in a meta-analysis of N-back fMRI tasks in healthy volunteers, typically activated regions in the brain during task performance compared to a visuomotor control are the frontal and parietal cortices including the lateral premotor, dorsal cingulate and medial premotor cortex, dorsolateral and ventro-lateral

prefrontal cortex, frontal poles, and medial and lateral posterior parietal cortex (Owen et al., 2005). However, certain deviations from this activation pattern during task performance have been repeatedly linked to bipolar disorder and psychoses unrelated to childbirth when compared to healthy controls (C. Chen et al., 2011; Fusar-Poli et al., 2012; Glahn et al., 2005; Minzenberg et al., 2009).

5.1.1 Working memory dysfunction in bipolar disorder

In patients with bipolar disorder, both hyper- and hypoactivations have been reported compared to healthy controls, which were sometimes accompanied by poorer and sometimes by similar task performance. Increases in brain activation, accompanied by poorer task performance when compared to healthy volunteers, have been reported in areas including the frontal cortex (e.g. dorsolateral prefrontal cortex, insula and anterior cingulate cortex), temporal and parietal cortices and subcortical structures (e.g. thalamus and caudate nucleus) (Adler, Holland, Schmithorst, Tuchfarber, & Strakowski, 2004; Drapier et al., 2008). Increases in activation within similar regions have also been reported in people at genetic risk of bipolar disorder (i.e. specifically in frontal and parietal cortices as well as in subcortical structures) (Drapier et al., 2008; Fusar-Poli et al., 2012; Thermenos et al., 2010; Thermenos et al., 2011). The activation seems to further increase with higher working memory load (Frangou, Kington, Rayment, & Shergill, 2008).

Other studies report that bipolar disorder patients show both decreases and increases in activations in certain brain areas compared to healthy volunteers; these are not necessarily accompanied by differences in performance (C. Chen et al., 2011; Jogia, Dima, & Frangou, 2012; Jogia, Dima, Kumari, & Frangou, 2012; Monks et al., 2004). Reduced activation has been reported in frontal regions (e.g. inferior frontal gyrus and insula), temporal and parietal cortices, and subcortical structure, while increases were shown in cingulate cortices and also in frontal and parietal areas (C. Chen et al., 2011; Jogia, Dima, & Frangou, 2012; Jogia, Dima, Kumari, et al., 2012; Monks et al., 2004).

Modulation of activation reported in bipolar disorder compared to healthy controls appears to be independent of mood state (Townsend, Bookheimer, Folland-Ross, Sugar, & Altshuler, 2010). Furthermore, modulation of activation seems to be

independent of gender, as no working memory related differences have been reported in either healthy individuals (Schmidt et al., 2009) or patients with bipolar disorder (Jogia, Dima, & Frangou, 2012; Jogia, Dima, Kumari, et al., 2012). In line with other findings in the cognitive domain it has been shown that when compared to patients with psychoses unrelated to childbirth, euthymic bipolar patients demonstrate activation differences intermediate between healthy controls and people with psychoses (L. S. Hamilton et al., 2009; Reichenberg, 2010; Reichenberg et al., 2009; Stefanopoulou et al., 2009).

5.1.2 Working memory dysfunction in psychoses unrelated to childbirth

As described earlier, working memory is severely impaired in psychoses unrelated to childbirth (Forbes, Carrick, McIntosh, & Lawrie, 2009; Reichenberg, 2010) and in the last decade considerable evidence has been collected to demonstrate that this is accompanied by aberrant brain activation (Glahn et al., 2005; Minzenberg et al., 2009). Similar to patients with bipolar disorder, hyper- and hypoactivations have been reported in the literature. A typical finding is that in N-back working memory paradigms, patients with psychoses unrelated to childbirth show, compared to healthy controls, reductions in the activation of certain frontal regions (e.g. dorsolateral and ventro-lateral prefrontal cortex, anterior cingulate cortex), but also in temporal, parietal and occipital cortices as well as subcortical areas (e.g. hippocampus, thalamus and putamen) (Glahn et al., 2005; Henseler, Falkai, & Gruber, 2009; Minzenberg et al., 2009).

However, decreases in activation have often been accompanied by increases in certain areas, including frontal areas (e.g. prefrontal cortex, anterior cingulate, insula), temporal and parietal cortices, and subcortical structures (D.M. Barch & Csernansky, 2007; Glahn et al., 2005; Minzenberg et al., 2009; Thormodsen et al., 2011). Differences in brain activation in frontal areas, including the dorsolateral prefrontal cortex, and in parietal areas have also been reported in people at high risk of developing psychoses unrelated to childbirth, with activation being intermediate between patients and healthy controls (Broome et al., 2009; Smieskova et al., 2012). Several authors have tried to find explanations for the apparent inconsistencies of

hyper- and hypoactivation found in bipolar disorder and psychoses unrelated to childbirth.

5.1.3 The effect of working memory load

Several attempts have been made to explain the hyper- and hypoactivation patterns of bipolar disorder and psychoses unrelated to childbirth when compared to healthy controls. For example, it has been proposed that some regions show a compensatory response (i.e. hyperactivation) to the hypoactivation in other regions (Minzenberg et al., 2009). However, the most accepted hypothesis is the “inefficiency hypothesis” (Callicott et al., 2003; Karlsgodt et al., 2009; M. A. Kim et al., 2010). According to this hypothesis, increasing task load correlates with increasing activation, but patients with psychoses unrelated to childbirth use greater prefrontal activation in order to achieve the same task performance as healthy controls (Callicott et al., 2003; Karlsgodt et al., 2009; M. A. Kim et al., 2010). It is also possible that at a higher working memory load, patients fail to sustain prefrontal activation (i.e. showing reductions compared to healthy controls following a u-shaped curve) with a subsequent decline in performance (Callicott et al., 2003; Karlsgodt et al., 2009; M. A. Kim et al., 2010). This hypothesis is supported by the fact that hypoactivation, especially in the dorsolateral prefrontal cortex, has been linked to worse performance in participants with psychoses unrelated to childbirth (D.M. Barch & Ceaser, 2012; Glahn et al., 2005; Perlstein, Carter, Noll, & Cohen, 2001). Nonetheless, in bipolar disorder increases in activation have been typically linked to poorer task performance, thus questioning the proposed hypothesis (Adler et al., 2004; Drapier et al., 2008).

In summary, working memory deficits that have been consistently reported in patients with bipolar disorder and psychoses unrelated to childbirth have been associated with differential brain activation compared to healthy controls, most significantly in the frontal cortex when assessed with the N-back task. Therefore, we expected to find a similar performance deficit and activation pattern in women at risk of postpartum psychosis. Specifically, we hypothesised that 1) women at risk of postpartum psychosis will show, in comparison to healthy controls, decreased brain activation in the dorsolateral prefrontal cortex during a working memory task

(primary hypothesis); 2) women at risk of postpartum psychosis will show, in comparison to healthy controls, differential brain activation as assessed with whole brain analysis (secondary hypothesis); 3) women at risk of postpartum psychosis will show, in comparison to healthy controls, impaired working memory performance (secondary hypothesis); 4) impairments in working memory and differences in brain activation in working memory will be more pronounced in women who had developed postpartum psychosis episodes, compared to women who had not developed postpartum psychotic episodes, and to healthy controls (secondary hypothesis). For these hypothesis the N-back task will be used.

5.2 Methods

5.2.1 Participants, design, analyses and procedures

The methods have been described in chapter 2. For information on the combined group analyses and sub group analyses please see chapter 2 and chapter 3.

5.2.2 N-back paradigm

This task comprised a stream of letters presented to the participant while lying in the MRI scanner. In the easiest level of difficulty, the participant had to respond if any letter was followed by the same letter (e.g. A-B-C-C). In this case the condition began with the instruction “one back”. In the next level of difficulty (i.e. two back), the participant had to respond if a letter was followed by the same letter with one distractor in between (e.g. A-B-C-B). Finally, in the three back condition (the highest level of difficulty) the participant had to respond if a letter was followed by the same letter with two distractors in between (e.g. A-B-C-A); see Figure 5.1.

During a control condition, the participant was asked to respond to the letter “X”. The task was presented in the form of a block design consisting of varying levels of difficulty. It included 12 blocks, each lasting 30 seconds and containing one instruction and 14 letters. Altogether the task lasted six minutes and 20 seconds with 180 stimuli with an inter-stimulus interval of two seconds.

Figure 5.1 The N-back task

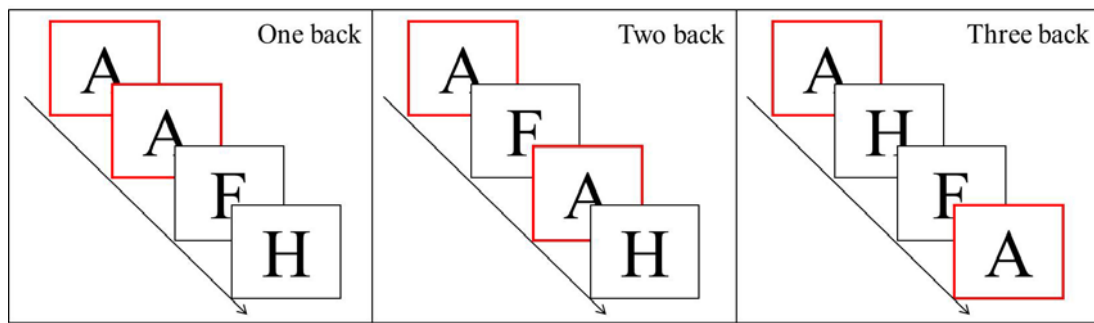


Figure 5.1 shows all three levels of difficulty of the N-back task with the easiest in the first column (one back), followed by the next level of difficulty in the middle column (two back) and the most difficult condition in the last column (three back).

5.2.3 Analysis

For a further description of the performance and imaging analyses please see chapter 2. The dependent variables for the behavioural analysis were the number of correct responses for the one-, two-, three back and the control condition and the reaction times of each condition. Specific contrasts of interest for the second-level model of the imaging analysis were the one, two and three back versus the control condition. Based on our hypotheses, we conducted a region of interest (ROI) analysis limited to the dorsolateral prefrontal cortex. This region was defined by commonly used anatomical landmarks of the right dorsolateral prefrontal cortex using the WFU PickAtlas tool in SPM (Bleich-Cohen et al., 2013; Glahn et al., 2005). We also conducted a whole brain analysis. In order to investigate possible correlations between activation and performance, we also examined the contrast between the three back and the two back condition with a ROI analysis. Regions were selected based on our results of this contrast and included the left midcingulum (MNI coordinates $x=-16$, $y=-24$, $z=38$), the right superior temporal gyrus (MNI coordinates $x=52$, $y=-4$, $z=-10$), and the left superior temporal gyrus (MNI coordinates $x=-48$, $y=-38$, $z=10$). Spherical masks with a radius of 10mm were created around the coordinates using the SPM toolbox MarsBaR. Regions of interest were further analysed using SPSS 20 for Windows.

5.3 Results

One healthy control was excluded from the analysis as her overall accuracy across all N-back conditions was only 50%, suggesting that she did not engage in the task. In

total 45 women were analysed (NPE=13, PE=12, healthy controls=20). Two participants had movement values greater than two mm/degrees (i.e. movement greater than one voxel). However, following inspection of the performance and imaging results, these participants did not show any significant differences in performance or activation and were therefore included in the analysis.

5.3.1 Performance results

There were no significant differences between groups (CGA and SGA) in accuracy or RT of the control condition (smallest $p=.34$).

5.3.1.1 Combined group analysis

There was no difference between groups (“at risk” versus healthy controls) on accuracy in the one back and two back conditions ($z=-.09$, $p=.92$; $z=-.44$, $p=.66$; respectively). However, there was a strong trend for a difference between groups on accuracy in the three back condition, with the “at risk” group performing worse than healthy controls ($z=-1.91$, $p=.06$). There was no significant difference between the “at risk” and healthy control group on false positives in the one, two, or three back conditions (smallest $p=.22$); see Figure 5.2 and Table 5.1.

Table 5.1 N-back performance (CGA)

Groups	“at risk” M (SD)	healthy controls M (SD)
Accuracy (%)		
Control	99 (2)	98 (7)
One back	97 (6)	97 (7)
Two back	85 (22)	91 (11)
Three back	69 (21)	82 (15)
False positives (%)		
One back	<1 (3)	<1 (4)
Two back	4 (6)	2 (5)
Three back	8 (10)	7 (10)
RT		
Control	515 (82)	490 (88)
One back	626 (130)	587 (135)
Two back	725 (142)	648 (122)
Three back	718 (144)	715 (161)

Table 5.1 shows the N-back scores of the “at risk” group and healthy controls on accuracy, false positive and reaction time. RT=reaction time. M=mean. SD=standard deviation.

5.3.1.2 Sub group analysis

There was no difference between groups (NPE, PE and healthy controls) on accuracy in the one back and two back conditions ($\chi^2(2,44)=.13$, $p=.94$; $\chi^2(2,44)=.55$, $p=.76$). Again, there was a trend for a difference between groups in accuracy in the three back condition ($\chi^2(2,44)=5.41$, $p=.07$), with the NPE group performing worse than healthy controls following Bonferroni correction ($z=-2.44$, $p=.05$). There was no significant difference between the NPE, PE and healthy control groups on false positives in the one, two, or three back conditions (smallest $p=.25$); see Figure 5.3 and Table 5.2.

Table 5.2 N-back performance (SGA)

Groups	NPE M (SD)	PE M (SD)	healthy controls M (SD)
Accuracy (%)			
Control	97 (9)	100 (0)	99 (32)
One back	97 (7)	97 (5)	97 (7)
Two back	80 (28)	87 (15)	91 (11)
Three back	65 (19)	72 (25)	82 (15)
False positives (%)			
One back	<1 (0)	<1 (3)	<1 (4)
Two back	2 (4)	5 (8)	2 (5)
Three back	9 (11)	6 (8)	7 (10)
RT			
Control	504 (75)	525 (91)	490 (88)
One back	644 (139)	619 (122)	587 (135)
Two back	731 (155)	730 (135)	648 (122)
Three back	670 (157)	772 (119)	715 (161)

Table 5.2 shows the N-back scores of the NPE, PE and healthy control groups on accuracy, false positive and reaction time. RT=reaction time. M=mean. SD=standard deviation.

5.3.1.3 Working memory load

The performance measure accuracy was analysed using Friedmans ANOVA. As shown in the graphs (Figures 5.2 and 5.3), there was a significant effect of working memory load across all groups ($\chi^2(2,45)=46.66$, $p<.01$) between both the one and two back, and the two and three back conditions, with the task getting increasingly more difficult ($z=-3.86$, $p<.01$; $z=-3.57$, $p<.01$; respectively).

Figure 5.2 Working memory load (CGA)

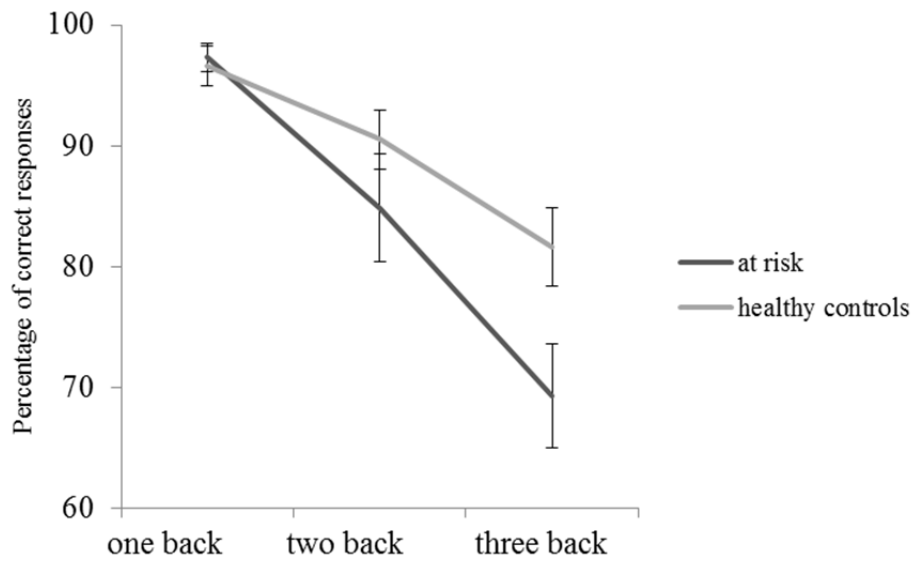


Figure 5.2 shows the mean N-back task performance of the “at risk” group and healthy controls on accuracy. The y-axis shows the mean performance. The error bars show the standard error of mean (SEM).

Figure 5.3 Working memory load (SGA)

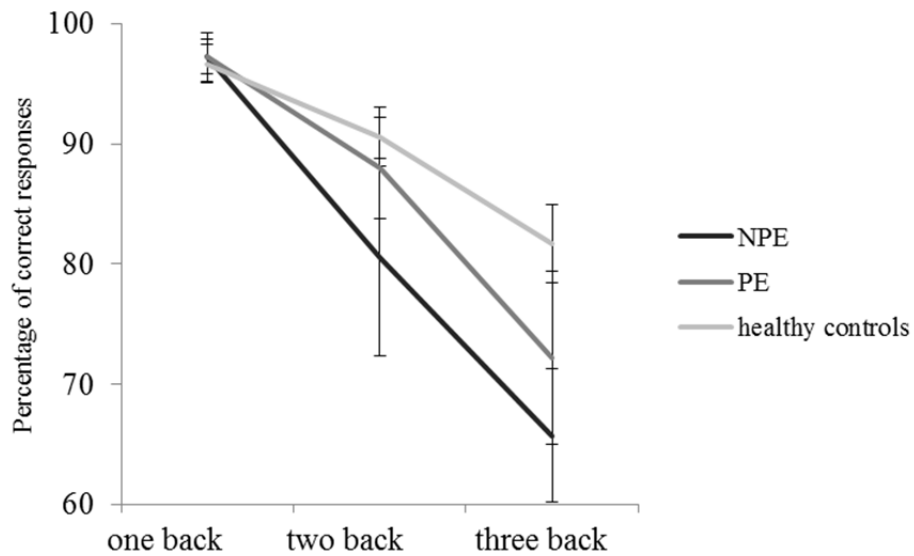


Figure 5.3 shows the mean N-back task performance of the NPE, PE, and healthy control groups on accuracy. The y-axis shows the mean performance. The error bars show the standard error of mean (SEM).

There was also a significant linear trend of false positives across all groups ($\chi^2(2,45)=29.95$, $p<.01$) between both the one and two back, and the two and three back conditions, with all women making increasingly more errors ($z=-2.35$, $p=.02$; $z=-3.41$, $p<.01$; respectively); see Figures 5.4 and 5.5.

Figure 5.4 False positives (CGA)

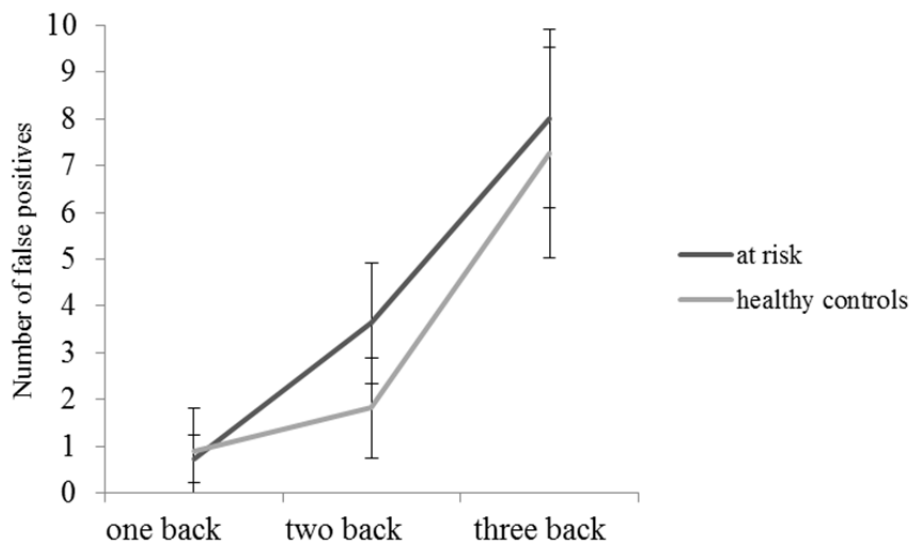


Figure 5.4 shows the mean N-back task performance of the "at risk" group and healthy controls on false positives. The y-axis shows the mean performance. The error bars show the standard error of mean (SEM).

Figure 5.5 False positive (SGA)

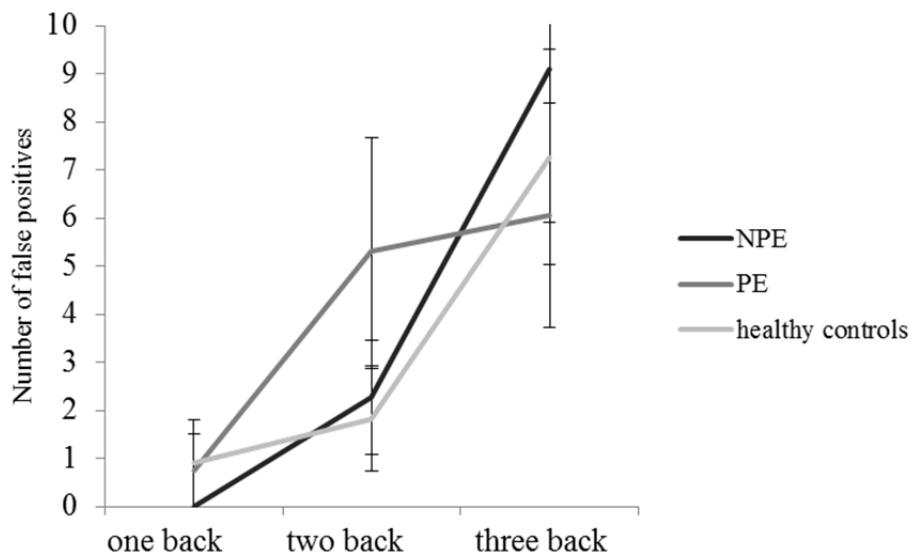


Figure 5.5 shows the mean N-back task performance of the NPE, PE and healthy control groups on false positives. The y-axis shows the mean performance. The error bars show the standard error of mean (SEM).

5.3.1.4 Reaction time

Reaction time was assessed using parametric tests. Using a repeated measures between groups ANOVA, there was no significant interaction effect in the combined analysis between group ("at risk" versus healthy controls) and RT (one, two, and

three back) ($F(2,42)=1.76$, $p=.18$) and no significant main effect between the “at risk” and healthy control groups ($F(1,43)=1.25$, $p=.27$). There was a linear effect of RT ($F(2,42)=17.61$, $p<.01$). However, when split into sub groups, there was a trend towards an interaction between group (NPE, PE and healthy controls) and RT (one, two, and three back) ($F(4,82)=2.51$, $p=.06$) with the NPE group having numerically a lower RT in the three back condition compared to the two back condition; see Figures 5.6 and 5.7. This indicates that women in the NPE group showed a relative faster response during the three back condition compared to the PE and healthy control groups.

Figure 5.6 Reaction time (CGA)

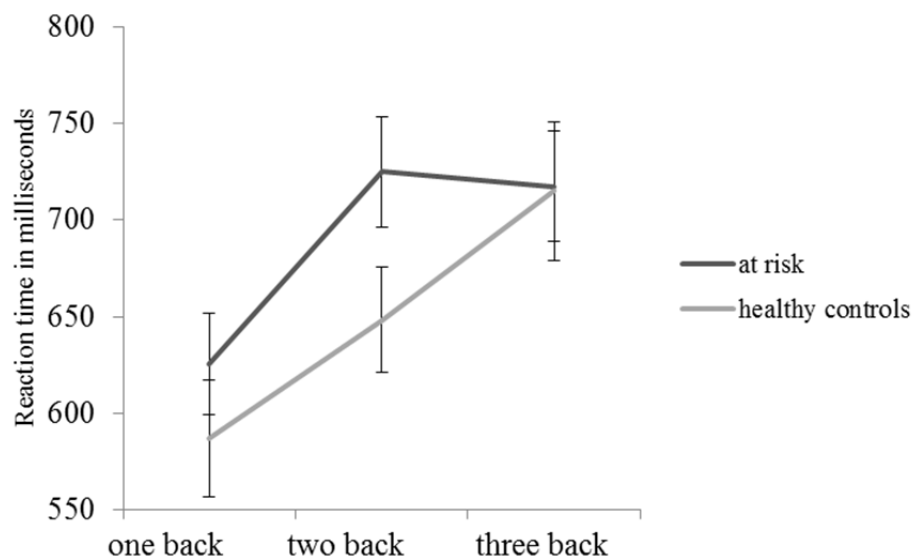


Figure 5.6 shows the mean reaction time of the “at risk” group and healthy controls during the one, two and three back conditions. The y-axis shows the mean reaction time. The error bars show the standard error of mean (SEM).

Figure 5.7 Reaction time (SGA)

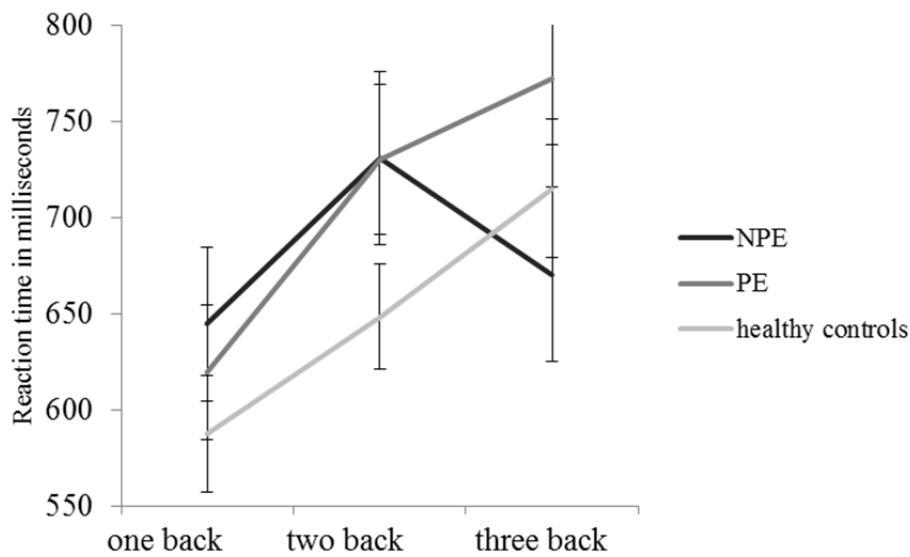


Figure 5.7 shows the mean reaction time of the NPE, PE, and healthy control groups during the one, two and three back conditions. The y-axis shows the mean reaction time. The error bars show the standard error of mean (SEM).

5.3.1.5 Additional analyses

There were no significant correlations between age, YMRS, HAM-D, PANSS, or length of illness and any of the performance measures within the “at risk” group (largest $r(25)=-.34$, smallest $p=.10$). There was also no significant effect of antipsychotic medication on performance when included into the models for the combined or sub group analysis as fixed factors (yes/no) (smallest $p=.24$).

As a further additional analysis we compared all women who were at risk of postpartum psychosis due to a diagnosis of bipolar disorder ($N=14$) or other diagnoses (i.e. schizoaffective disorder, postpartum psychosis or family history) ($N=11$) and healthy controls ($N=20$). There were no significant group differences in accuracy or false positives (smallest $p=.10$). There was a trend towards an interaction between group (bipolar, “other” and healthy controls) and RT (one, two, and three back) ($F(4,84)=2.12$, $p=.09$) with women in the bipolar group having numerically a lower RT in the three back condition compared to the two back condition. This indicates that women in the bipolar group showed a relative faster response during the three back condition compared to the other “at risk” and healthy control groups.

5.3.2 *Imaging results*

Two ROI analyses of the dorsolateral prefrontal cortex and two full-factorial ANOVA models were conducted with 1) group (“at risk” versus healthy controls) as between subject factor and load (one-, two-, and three-back) as within subject factor for the combined group analysis (2x3) and 2) group (NPE, PE and healthy controls) as between subject factor and load (one-, two-, and three-back) as within subject factor for the sub group analysis (3x3).

5.3.2.1 *N-back working memory network*

As a first analysis, we confirmed that the task robustly elicited the established network of regions reported in the literature in our participants, including the frontal and parietal areas (Minzenberg et al., 2009; Owen et al., 2005). For this, we performed an analysis looking at brain regions activated by the one-, two-, and three-back conditions across groups in the 2x3 model (CGA); see Table 5.3 and Figure 5.8.

Table 5.3 The N-back task network for one-, two-, and three-back conditions across all groups

Area	x	Y	z	BA	Voxels	Z	Pcor
R Mid Frontal	34	2	60	6	2932	7.27	<.001
L Mid Frontal	-40	50	12	46	345	6.30	<.001
L Precentral	-44	0	30	6	2145	7.54	<.001
R Insula	32	24	-4	47	301	6.83	<.001
L Insula	-32	22	0	47	179	5.56	<.001
R Inf Temporal	52	-52	-14	20	50	4.97	=.005
R Angular	30	-64	44	7	3753	>7.54	<.001
L Parietal Sup	-24	-68	46	7	2748	>7.54	<.001
L Inf Occipital	-46	-62	-14	37	34	4.69	=.009
L Thalamus	-14	-22	18	27	6	4.49	=.029

Table 5.3 shows the brain regions activated during the contrast “all back>control”. X, y, and z refer to the MNI coordinates. BA refers to the Brodmann area and Z and Pcor give the Z value and the significant p-value (corrected for multiple comparisons on the basis of family wise error (FWE)). L refers to left and R to right side of the brain.

Figure 5.8 The N-back task network for one-, two-, and three-back conditions across groups

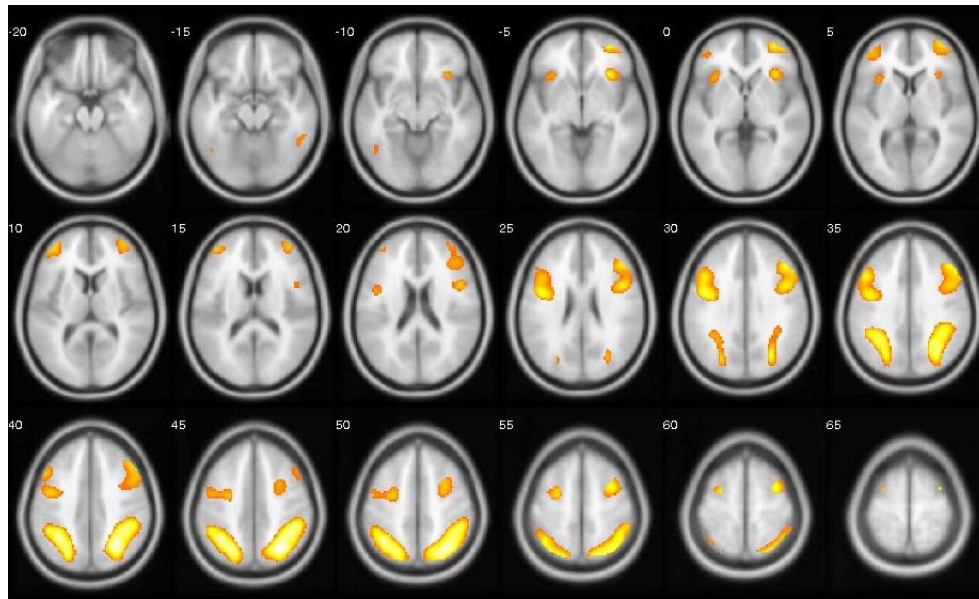


Figure 5.8 shows the brain regions activated during the contrast “all back>control” overlaid on a high resolution T1-weighted template image in Montreal Neurological Institute space. Numbers refer to z coordinates. Voxels are corrected for multiple comparisons on the basis of family wise error (FWE). Left is the left and right the right side of the brain.

5.3.2.2 Working memory load

As a next step, we investigated the linear effect of increasing working memory load across groups and found modulations in areas depicted in Table 5.4 with increasing task demands in the 2x3 model (CGA); see Figures 5.9, 5.10, and 5.11.

Table 5.4 The effect of increasing working memory load across groups

Area (>10 voxels)	x	Y	z	BA	Voxels	Z	Pcor
L Tri Inf Frontal	-44	14	28	48	3312	7.02	<.001
R Mid Frontal	40	36	22	45	3832	6.55	<.001
L Mid Frontal	-32	46	8	10	336	5.62	<.001
R Ant Cingulate	14	28	22	32	61	5.41	=.001
R Insula	38	-16	18	48	96	5.24	=.002
R Caudate	16	0	14	NA	118	5.27	=.001
L Caudate	-18	-2	14	NA	65	4.99	=.005
L Heschl	-54	-12	8	48	99	5.50	<.001
R Sup Temporal	60	-8	6	22	180	5.68	<.001
L Inf Parietal	-40	-58	50	39	2266	6.52	<.001
R Lingual	20	-58	0	19	23	4.57	=.030
R Fusiform	24	-40	-12	30	31	4.74	=.014
R Precuneus	4	-56	28	23	120	5.04	=.004
R Precuneus	16	-70	50	7	2612	6.48	<.001
R Cuneus	10	-94	28	18	47	5.13	=.002

Table 5.4 shows the brain regions modulated during the contrast three-back>two-back>one-back. X, y, and z refer to the MNI coordinates. BA refers to the Brodmann area and Z and Pcor give the Z value and the significant p-value (corrected for multiple comparisons on the basis of family wise error (FWE)). L refers to left and R to right side of the brain.

Figure 5.9 The effect of increasing working memory load across all groups

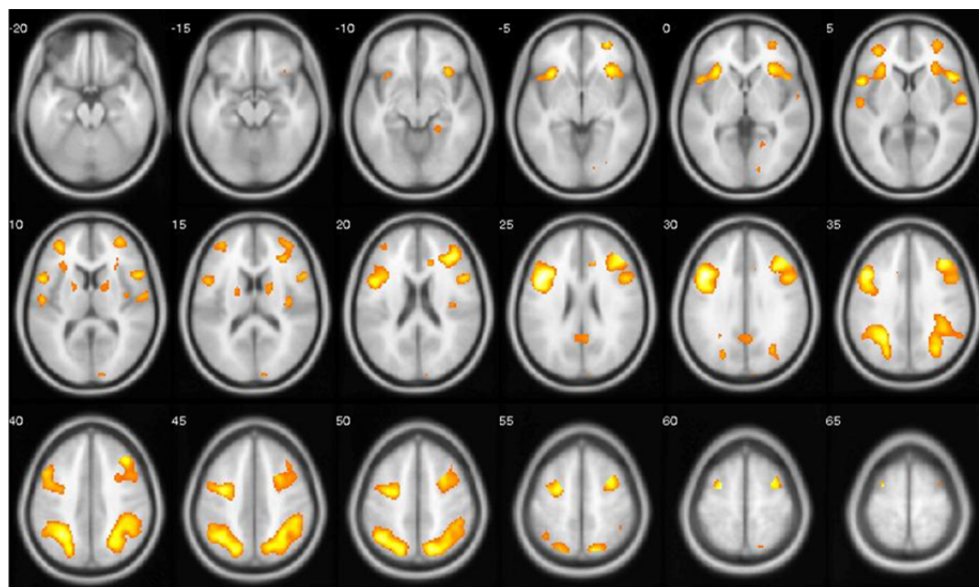


Figure 5.9 shows the brain regions activated during the contrast three-back>two-back>one-back overlaid on a high resolution T1-weighted template image in Montreal Neurological Institute space. Numbers refer to z coordinates. Voxels are corrected for multiple comparisons on the basis of family wise error (FWE). Left is the left and right the right side of the brain.

Figure 5.10 The effect of increasing working memory load (CGA)

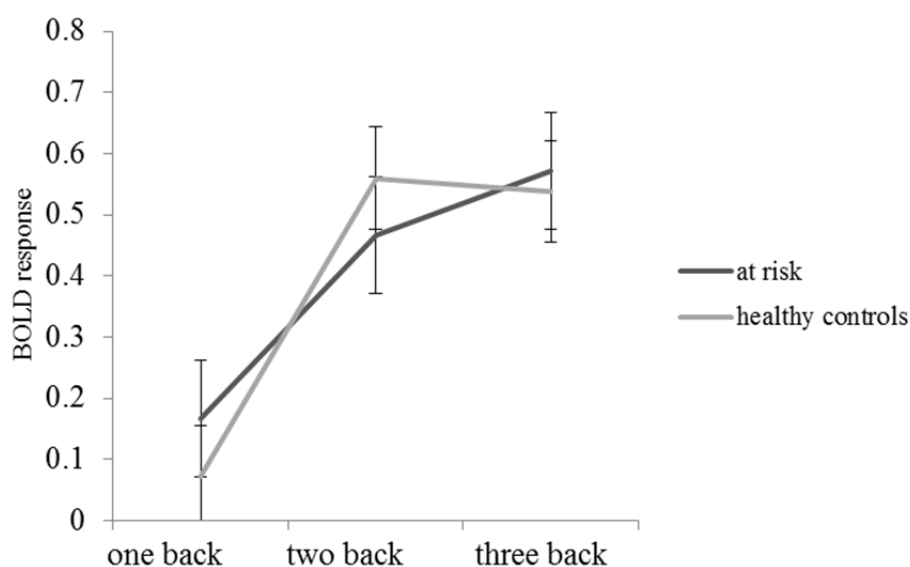


Figure 5.10 shows the mean BOLD increase in activation in the “at risk” group and healthy controls for the three-back>two-back>one-back contrast in the left inferior frontal cortex (MNI coordinates: $x=-44$, $y=14$, $z=28$). The y-axis shows the mean BOLD response. The error bars show the standard error of mean (SEM).

Figure 5.11 The effect of increasing working memory load (SGA)

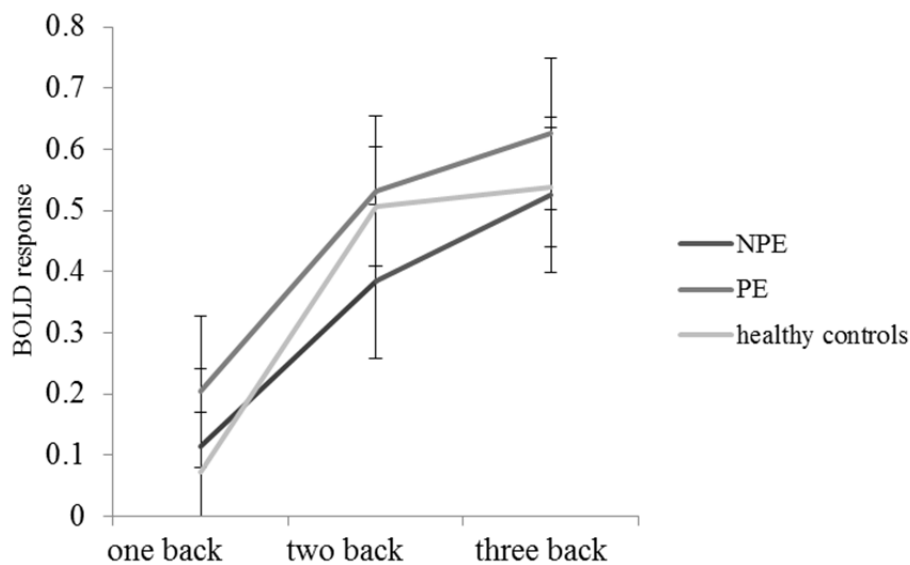


Figure 5.11 shows the mean BOLD increase in activation in the NPE, PE and healthy control groups for the three-back>two-back>one-back contrast in the left inferior frontal cortex (MNI coordinates: $x=-44$, $y=14$, $z=28$). The y-axis shows the mean BOLD response. The error bars show the standard error of mean (SEM).

5.3.2.3 Group versus load interactions

There were no significant group differences in our ROI analyses. Furthermore, there were no supra-threshold clusters when we looked at an overall interaction between group and load for either the combined or sub group analyses. There were also no supra-threshold clusters for the main effect of group for the combined or sub group analyses. However, when we compared the group versus load separately for the “one- versus two-back” and “two- versus three-back” conditions in order to assess increased working memory load, with a special importance of the “two- versus three-back”, we found a significant interaction in the latter comparison between the “at risk” and healthy control groups, with the “at risk” group showing a lower activation during the two back, but higher activation during the three back condition. This pattern also emerged when we performed the sub group analysis, as the NPE and PE groups showed a similar activation profile. However, results only were statistically significant for the NPE group; see Tables 5.5 and 5.6 and Figures 5.12, 5.13, and 5.14.

Table 5.5 Group versus load (two- and three-back) interaction (CGA)

Area	x	Y	z	BA	Voxels	Z	Pcor
L Mid Cingulum	-16	-24	38	23	669	4.42	=.007
R Sup Temporal	52	-4	-10	21	667	4.26	=.008
L Sup Temporal	-48	-38	10	42	695	3.84	=.066

Table 5.5 shows the brain regions activated during the contrast two-back versus three-back in the “at risk” group versus healthy controls. X, y, and z refer to the MNI coordinates. BA refers to the Brodmann area and Z and Pcor give the Z value and the significant p-value (corrected for multiple comparisons on the basis of cluster extent ($p < .001$)). L refers to left and R to right side of the brain. The activation in the left mid cingulum remained significant after FWE correction ($Z = .42$, $p = .04$).

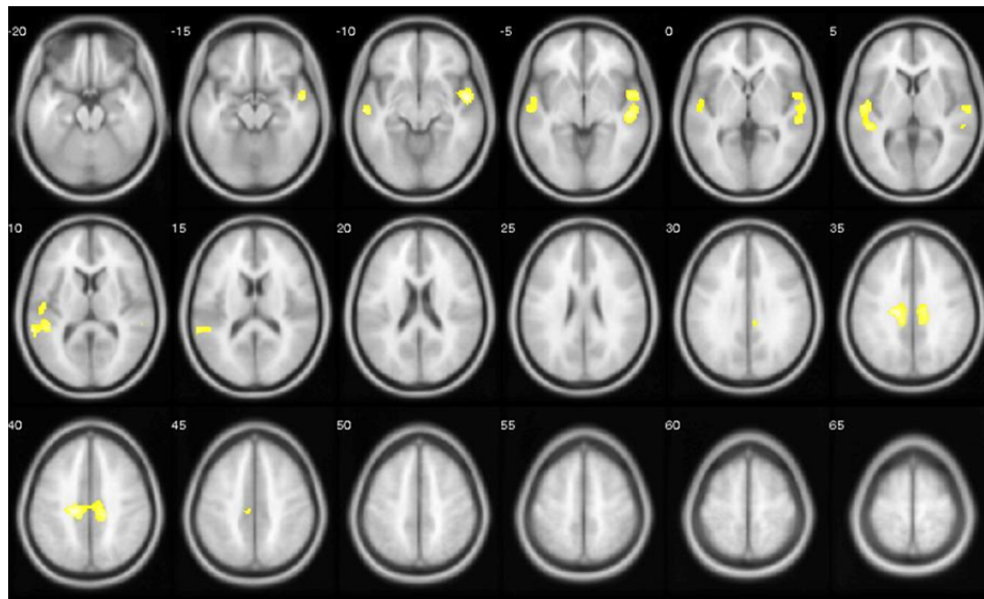
Figure 5.12 Group versus load (two- and three-back) interaction (CGA I)

Figure 5.12 shows the brain regions activated during the contrast two-back versus three-back in the “at risk” group versus healthy controls overlaid on a high resolution T1-weighted template image in Montreal Neurological Institute space. Numbers refer to z coordinates. Voxels are corrected for multiple comparisons on the basis of cluster extent ($p < .001$). Left is the left and right the right side of the brain.

Figure 5.13 Group versus load (two- and three-back) interaction (CGA II)

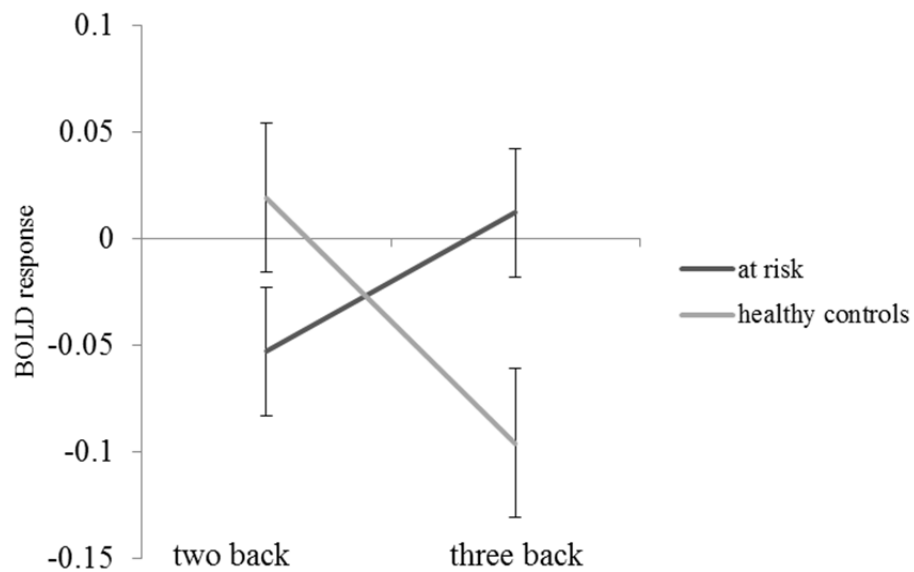


Figure 5.13 shows the interaction between the mean BOLD response of the “at risk” and the healthy control groups, with the “at risk” group shows a lower activation during the two back, but higher activation during the three back condition compared to healthy controls in the left mid cingulum (MNI coordinates: $x=-16$, $y=-24$, $z=38$). The y-axis shows the mean BOLD response. The error bars show the standard error of mean (SEM).

Figure 5.14 Group versus load (two- and three-back) interaction (SGA)

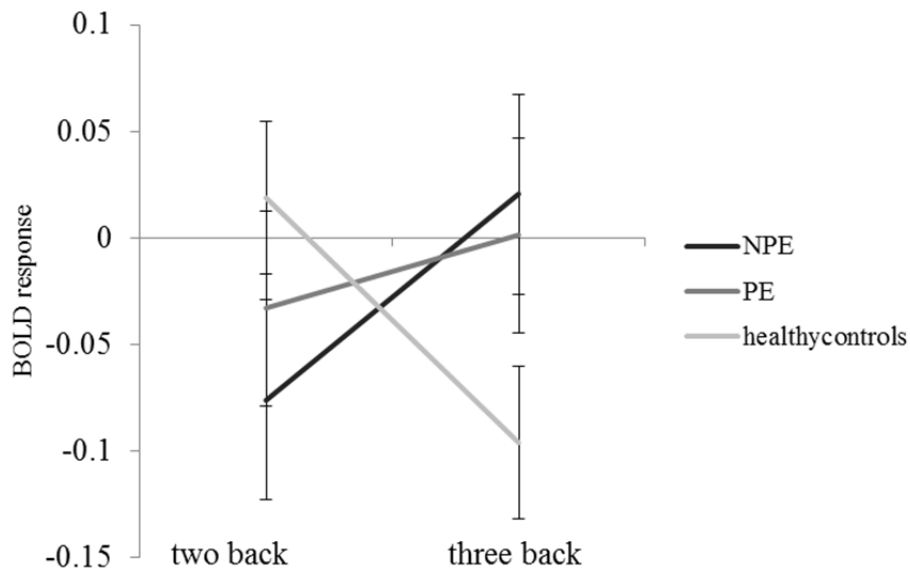


Figure 5.14 shows the interaction between the mean BOLD response of the NPE, PE and healthy control groups, with the NPE and PE groups shows a lower activation during the two back, but higher activation during the three back condition compared to healthy controls in the left mid cingulum (MNI coordinates: $x=-16$, $y=-24$, $z=38$). The y-axis shows the mean BOLD response. The error bars show the standard error of mean (SEM).

Table 5.6 Group versus load (two- and three-back) interaction (SGA)

Area	x	Y	z	BA	Voxels	Z	Pcor
NPE group							
L Mid Cingulum	-18	-26	40	23	353	4.07	=.072
L Sup Temporal	-48	-40	12	42	631	4.01	=.013
PE group							
R Precuneus	4	-48	16		368	4.06	=.006

Table 5.6 shows the brain regions activated during the contrast two-back versus three-back in the NPE and PE group versus healthy controls. X, y, and z refer to the MNI coordinates. BA refers to the Brodmann area and Z and Pcor give the Z value and the significant p-value (corrected for multiple comparisons on the basis of cluster extent ($p < .001$)). L refers to left and R to right side of the brain.

The significant interaction was driven by a deactivation in the three areas in the healthy control group as assessed with a one sample t-test; see Table 5.7.

Table 5.7 Deactivations in the healthy control group for the contrast three-back>two-back

Area	x	Y	z	BA	Voxels	Z	Pcor
L Mid Cingulum	-10	0	36	24	147	4.16	=.252
R Sup Temporal	54	-4	-10	22	795	4.38	=.001
L Sup Temporal	-48	-10	8	48	553	4.53	=.004

Table 5.7 shows the brain regions deactivated during the contrast three-back>two-back in the healthy controls group. X, y, and z refer to the MNI coordinates. BA refers to the Brodmann area and Z and Pcor give the Z value and the significant p-value (corrected for multiple comparisons on the basis of cluster extent ($p < .001$)). L refers to left and R to right side of the brain.

5.3.2.4 Additional analyses

We did not find any supra-threshold group differences in frontal regions using the SPM WFU PickAtlas ROI approach. We further investigated whether the differences in activation found in the left midcingulate cortex and the right and left superior temporal gyrus correlated with the task performance. For that, we conducted a ROI analysis of these three regions for the contrast “three back” greater “two back” and correlated the activations with the behavioural difference scores of the three and two back, the three back and overall performance within the “at risk” group. There were no significant correlations of the activation in the left midcingulate cortex or the right and left superior temporal gyrus with any of behavioural performance measures (largest $r(25) = -.26$, smallest $p = .21$). There were also no correlations of activation in the left midcingulate cortex or the right or left superior temporal gyrus with age, YMRS, HAM-D, PANSS, or length of illness (largest $r(25) = .33$, smallest $p = .11$). Antipsychotic medication (yes/no), age, scores of the YMRS, HAM-D, PANSS, or length of illness did not have significant effects on the imaging results when included as covariates in the full-factorial models.

As a further additional analysis we compared all women who were at risk of postpartum psychosis due to a diagnosis of bipolar disorder or other diagnoses (i.e. schizoaffective disorder, postpartum psychosis or family history) and healthy controls. When we compared the group versus load for the “two- versus three-back” conditions, we found a significant interaction between the bipolar and healthy control groups, with the bipolar group showing a relative lower activation during the two back, but relative higher activation during the three back condition in the right mid cingulum (BA=23, x=10, y=-30, z=36, voxels=2626, Z=4.48, Pcor<.001) and the left superior temporal gyrus (BA=48, x=-54, y=-16, z=8, voxels=869, Z=4.06, Pcor=.003). When we compared the other “at risk” diagnoses to healthy controls we also found a similar modulation of the left mid cingulum (BA=23, x=-18, y=-20, z=36, voxels=140, Z=4.21, Pcor=.32) and the left postcentral gyrus (BA=2, x=-40, y=-38, z=60, voxels=118, Z=3.71, Pcor=.39). However, results were only statistically significant for the bipolar group.

5.4 Discussion

In this chapter, the working memory performance and accompanying brain activation were investigated in women at risk of postpartum psychosis using an N-back fMRI working memory paradigm. We expected that 1) women at risk of postpartum psychosis will show, in comparison to healthy controls, decreased brain activation in the dorsolateral prefrontal cortex during a working memory task (primary hypothesis); 2) women at risk of postpartum psychosis will show, in comparison to healthy controls, differential brain activation as assessed with whole brain analysis (secondary hypothesis); 3) women at risk of postpartum psychosis will show, in comparison to healthy controls, impaired working memory performance (secondary hypothesis); 4) impairments in working memory and differences in brain activation in working memory will be more pronounced in women who had developed postpartum psychosis episodes, compared to women who had not developed postpartum psychotic episodes, and to healthy controls (secondary hypothesis).

5.4.1 Summary of findings

In all groups there was an effect of working memory load on performance, showing decreasing task accuracy and increasing rate of false positives and reaction time with increasing task difficulty. As expected in our secondary hypothesis, women at risk of postpartum psychosis showed a trend towards an impaired task performance in the most difficult condition of the N-back task placing the highest working memory load demands on participants. Differently from our prediction, however, was that the NPE group performed the worst, showing a faster reaction time than healthy controls with the PE group performing on an intermediate level. We could not confirm our primary hypothesis, as there was no decreased brain activation in the dorsolateral prefrontal cortex of the “at risk” group compared to healthy controls. However, we found a relative increase in activation as evidenced by a significant interaction between the “at risk” and healthy control groups in the left midcingulate cortex and the bilateral superior temporal cortex following the whole brain analysis. The “at risk” group showed a lower activation during the two back, but higher activation during the three back condition compared to healthy controls. The PE group showed a similar activation profile as the NPE group, but with intermediate activation levels compared to the NPE and healthy control groups. While we had a large enough sample size in order to assess the primary hypothesis, we would like to acknowledge that for the secondary hypotheses, including the whole brain and the performance analyses, the study may have been underpowered.

5.4.2 Performance

The effect of working memory load on task accuracy, false positives and reaction time found across all groups is in agreement with the N-back task literature (Jogia, Dima, & Frangou, 2012; Jogia, Dima, Kumari, et al., 2012; Schmidt et al., 2009). In addition, the strong trend of an impairment in task performance in the “at risk” group is consistent with previous results demonstrating an impairment in working memory performance in bipolar disorder (Adler et al., 2004; Drapier et al., 2008). There are studies that do not report performance deficits using a two-back design (Broome et al., 2009; Monks et al., 2004; Thermenos et al., 2011). One difference to these studies is that in our study a three-back task design, adding a higher level of

difficulty, was employed (Broome et al., 2009; Monks et al., 2004; Thermenos et al., 2011). It is possible that the performance difference was only evident at this level of task difficulty. This suggestion is supported by the fact that our two back performance results were similar to earlier studies (Broome et al., 2009; Monks et al., 2004; Thermenos et al., 2011).

In contrast to our prediction, it was the PE group that showed intermediate levels of accuracy between healthy controls and the NPE group. Additionally, the decrease in accuracy was accompanied by a decrease in reaction time only in the NPE group, suggesting that women in this group may have used a different response strategy, such as a greater speed-accuracy trade-off for the most difficult task condition, compared to women in both the healthy control and PE groups. A more rapid response to the task under greater loads has been previously found in a working memory study on schizophrenia (M. A. Kim et al., 2010). Alternatively, women in the NPE group may have been less engaged in the task during the three back condition due to higher task demands. However, accuracy was still above chance level, suggesting that, on average, women in the NPE group were following task instructions.

In summary, women at risk of postpartum psychosis seem to have performance deficits in verbal working memory. Similarly to our findings in the verbal memory domain, this result seems mainly driven by women with previous non-postpartum episodes, while women with postpartum episodes show intermediate performance levels. Furthermore, it is possible that women in the non-postpartum group employed a different strategy during the three back condition, possibly due to a deficit in coping with the task demands. This is an interesting hypothesis, which should be validated in larger sample sizes in the future.

5.4.3 *Imaging results*

We evaluated a general N-back memory network across all groups as a previous meta-analysis found that controls and people with psychosis activate a qualitatively similar network during cognitive task performance (Minzenberg et al., 2009; Owen et al., 2005). The task elicited the typical N-back working memory network and activation for increasing load in our participants, including the frontal and parietal

areas (Minzenberg et al., 2009; Owen et al., 2005), confirming that the task manipulation worked. We did not find evidence to confirm our primary hypothesis. Based on our power calculation, the study should have had enough power to detect an effect in this sample. Yet, the sample size was still relatively small and therefore our study may have been underpowered. A better prediction of an accurate power would have been possible with pilot data (Mumford, 2012). As this current study is the first one conducted in women at risk of postpartum psychosis, these findings can be taken as preliminary and used as pilot data on which a power calculation for future investigations can be based. Therefore it contributes important knowledge and data to research in postpartum psychosis.

It could also be that there is no significant difference in dorsolateral prefrontal cortex functioning in women at risk of postpartum psychosis compared to healthy controls and therefore, we could not detect an effect. Another explanation for the lack of finding of a significant difference in the dorsolateral prefrontal cortex may be that in our study only women took part. According to our knowledge, only one study has reviewed gender effects in bipolar disorder, stating that there is an absence of fMRI studies reporting on sex differences (Jogia, Dima, & Frangou, 2012). It is possible that differences in frontal brain activation during working memory assessments are more pronounced in males diagnosed with bipolar disorder. In line with a recent review on working memory dysfunction in bipolar disorder assessed by the N-back task, our whole brain analysis showed significant activation differences in regions, which have been found to be implicated in working memory (Cremaschi et al., 2013). There was a relative increase in activation in the left midcingulate cortex and the bilateral temporal cortex in the “at risk” group compared to healthy controls between the two and three back conditions, as evidenced by a significant interaction. This relative change in activation in the midcingulate cortex and the bilateral temporal cortex may reflect an increase in task demands, possibly proving more challenging for the “at risk” group than healthy controls due to dysfunction in promoting task efficiency and resulting in a strategy change in this group. In the following sections the potential roles of the midcingulate cortex and the bilateral temporal cortex will be further discussed.

5.4.3.1 Potential role of the midcingulate cortex

The midcingulate cortex has been found to be involved in motor response selection, producing different combinations of actions and outcome (Vogt, Berger, & Derbyshire, 2003), especially in tasks involving cues which may cause conflict such as divided attention and stroop tasks (Derbyshire, Vogt, & Jones, 1998; van Veen & Carter, 2002). It could be that a relative increase in activation in the midcingulate activation of the “at risk” group reflects an increase in the difficulty of linking the cognitive demands of the more challenging task condition with the appropriate motor response. It has been reported previously that midcingulate cortex activity increases with task difficulty (Vogt, 2009). However, the actual motor response required during the three back condition is not different to the other task conditions, suggesting that the increase was not related to the difficulty of linking the cognitive demands with the motor response. Furthermore, this hypothesis would also predict an increase in activation with difficulty in healthy controls and they showed a decrease in our study.

It is also possible that the increase in activation, specifically driven by the NPE group, is linked to a change in strategy use during the three back condition. It has been reported that the midcingulate cortex is activated during changes in responses and the reorganisation of behaviour for changing rewards (Bush et al., 2002; Vogt, 2009; Vogt et al., 2003). In addition, lesions in the anterior and midcingulate cortex and an increase in activation in these areas have been associated with task switching (Rushworth, Hadland, Gaffan, & Passingham, 2003; Rushworth, Hadland, Paus, & Sipila, 2002). Given that we see a change in reaction time combined with a trend towards a worse performance, this possibility should be further investigated. In order to further assess possible changes in strategy use in postpartum psychosis under difficult task conditions, future studies should manipulate difference components of the task or employ paradigms which directly assess task switching (Rushworth et al., 2003; Rushworth et al., 2002).

Finally, it has been reported that the dorsal anterior cingulate cortex bordering on the midcingulate cortex promotes task efficiency by speeding up responses (Sheth et al., 2012). Yet, in situations with changing conditions responses are slowed down in order to ensure accuracy (Sheth et al., 2012). It may be that this process in women at risk of postpartum psychosis is dysfunctional, and that they respond with a decrease

in reaction time to more difficult task conditions. This dysfunction could be accompanied by an increase in midcingulate activation in the NPE group. Taken together, our data suggest that the aberrant activation in the midcingulate cortex in the “at risk” group is most likely linked to a change in strategy use or a deficit in promoting task efficiency in this group.

5.4.3.2 Potential role of the bilateral temporal cortex

An increased activation in the right superior and middle temporal gyri has been reported in other fMRI N-back working memory studies in bipolar disorder and psychoses unrelated to childbirth compared to healthy controls (Adler et al., 2004; Jogia, Dima, & Frangou, 2012; M. A. Kim et al., 2010). This greater activation has been associated with increases in task demands in studies using other verbal tasks (Ragland et al., 2008). The view that an increased activation may be linked to higher task demands, possibly more challenging for the “at risk” group, is supported by the lower task performance of the “at risk” group in the current study. However, again, this hypothesis would also predict an increase in activation with difficulty in healthy controls and they showed a decrease in our study.

Alternatively, the faster reaction time of the NPE group in the three back condition could be an indication of a strategy change in this group for the more difficult task condition, resulting in the relative increase of activation in the temporal lobes. An increased activation in the bilateral temporal cortex during a working memory task correlated previously with a faster reaction time in patients with psychosis compared to healthy controls (M. A. Kim et al., 2010). This increased activation was further proposed to be associated with an attempt of patients to maintain high accuracy during the more demanding task conditions (M. A. Kim et al., 2010). Similarly, in our study, the increased activation in the “at risk” group was also accompanied by a decrease in reaction time, indicating that the temporal cortex may have been used for a more rapid response to the task in order to compensate for performance deficits. However, given that there was a trend for the “at risk” group to show a lower task performance in the three back condition and the lack of a correlation between imaging and behavioural performance measures, this explanation seems less plausible.

Another possibility is that the “at risk” group showed a functional compensation for potential structural abnormalities as temporal lobes volumetric grey matter reductions have been reported in first episode as well as chronic schizophrenia (Kuroki et al., 2006; Onitsuka et al., 2004). In order to prove this hypothesis, future analysis should look at the association between the functional data of the task and volumetric measures. Nonetheless, lesion studies have found that language comprehension is impaired in people with lesions in the temporal cortex (Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004), potentially influencing verbal working memory activation and performance.

Finally, the temporal cortex has previously been reported to be employed for maintenance of phonological information during a working memory task (Strand, Forssberg, Klingberg, & Norrelgen, 2008). Therefore, the relative increase in activation in the bilateral temporal lobe could be associated with the increasing maintenance demands due to the longer delay between targets in the three back condition. This may have been more challenging for the “at risk” group than the healthy controls due to a working memory dysfunction. However, the task used by Strand and colleagues was a phonological working memory paradigm and therefore it is not clear to what extent the results are generalisable to other working memory paradigms. In summary, the bilateral temporal lobes show an increase in activation as task demands increase during the three back condition. This may indicate that this condition was more challenging for the “at risk” group than the healthy control group, resulting in a faster reaction time and an increase in temporal lobe activation. Future studies should assess the precise role of the temporal cortex in working memory paradigms.

5.4.4 Additional analysis

There were no correlations between age or clinical measures and performance or imaging results. Furthermore, taking antipsychotic medication did not seem to influence performance or imaging results. There were also no correlations between in performance and imaging results.

5.4.4.1 Impact of bipolar disorder

We also assessed the influence of a bipolar disorder diagnosis on performance and imaging results. Women with bipolar disorder did not perform worse compared to healthy controls or women who were “at risk” due to other diagnoses. Nonetheless, we did find a trend towards a faster reaction time during the three back condition. Women with bipolar disorder also showed a significant lower activation during the two back, but higher activation during the three back conditions in the right mid cingulum and the left superior temporal gyrus compared to healthy controls. This indicates that the findings in the NPE group were mainly driven by women with a bipolar disorder diagnosis. However, women with “other at risk diagnoses” also showed a non-significant modulation of the left mid cingulum and the left postcentral gyrus compared to healthy controls. These results suggest that women with bipolar disorder show a strategy change or difficulty in promoting task efficiency during the most difficult task condition, which is accompanied by an increase in activation in the midcingulate and the temporal cortices. Nonetheless, there is an indication that women who are at risk of postpartum psychosis due to other diagnoses, with a majority of women in the group who have suffered from a postpartum episode, show aberrant activation in similar areas. The more subtle modulation in the other “at risk” group may have been affected by a reduced statistical power. Unfortunately, we did not have a separate group with bipolar disorder unrelated to childbirth, which would have been important for an independent confirmation of the bipolar hypothesis. Taken together, our results suggest that women who have suffered from postpartum psychosis show similar working memory deficits in their cognitive profile to those with bipolar disorder.

5.4.5 Conclusion

Women at risk of postpartum psychosis show indications of a performance deficit in verbal working memory as predicted by our secondary hypothesis. This was accompanied by an increase in activation in the midcingulate cortex and the bilateral temporal lobe compared to healthy controls. As the differences we have found in the midcingulate cortex and the bilateral temporal lobe were part of the whole brain analyses, they will need to be validated in larger sample sizes in the future as they

would not survive overall multiple comparison corrections ($P < 0.001$) of this study. Nonetheless, this increased activation likely reflects an increase in the task demands, which may have been more challenging for the “at risk” group due to dysfunction in promoting task efficiency, resulting in a strategy change in this group. Furthermore, results indicate that women who have suffered from postpartum episodes show a similar cognitive profile to women with non-postpartum episodes.

6. Chapter: Facial emotion processing

In this chapter, an overview of the relevant fMRI literature on facial emotion processing will be presented. Then, the Ekman faces task, used in the current study, and additional details of the analysis will be described. This will be followed by the presentation of the performance and imaging results and their discussion in the context of the existing literature.

6.1 Introduction

With the exception of one case study on a monozygotic twin pair discordant for postpartum psychosis, no studies have been conducted in postpartum psychosis assessing emotional processing (Fahim et al., 2007). In this specific study a decreased activation in the orbital frontal gyrus was found in the sibling with history of postpartum psychosis compared to her sister, indicating a disturbance in the integration of emotionally relevant information (Fahim et al., 2007). Dysfunctional emotional processing is one of the key impairments in bipolar disorder and psychoses unrelated to childbirth (Bediou et al., 2005; Brüne, 2005; Y. Chen et al., 2012; Hoertnagl et al., 2011; Kohler et al., 2010; Malhi et al., 2007; Rocca et al., 2009). While the impairment in emotional processing seems to be task and modality independent, most studies concentrated on a deficit in facial emotion processing (Aleman & Kahn, 2005; V. Bozikas et al., 2007; Chan, Li, Cheung, & Gong, 2010; C. Chen et al., 2011; Edwards, Jackson, & Pattison, 2002; Hooker & Park, 2002; Kohler et al., 2010).

The Ekman faces paradigm is the most often used paradigm in the fMRI literature to assess facial emotion processing (Fusar-Poli et al., 2009) and was therefore chosen in this study. It typically depicts 60 faces portraying specific emotions (e.g. happy, fear, anger, sadness). Brain regions involved in facial processing independent of emotional valence are visual areas (e.g. fusiform gyrus), limbic and subcortical areas (e.g. the amygdala), and prefrontal and temporoparietal areas, as reported by a recent meta-analysis of 105 studies in healthy volunteers (Fusar-Poli et al., 2009). During conditions portraying specific emotions, such as fearful, happy or sad faces, a specific involvement of the amygdala has been found, while during angry and

disgusted faces the insula seems to play a more important role (Fusar-Poli et al., 2009; Moriguchi et al., 2005; M. L. Phillips et al., 1997).

Facial emotion paradigms including the Ekman faces task can be presented explicitly or implicitly (C. Chen et al., 2006; Gorno-Tempini et al., 2001). During explicit recognition, participants usually have to guess a specific facial emotion shown and potentially also give a rating of the emotional intensity (Goghari & Sponheim, 2012; Hoernagel et al., 2011; Li et al., 2012). The explicit paradigm is frequently used during studies aiming to measure differences in performances of emotion recognition between certain groups, while implicit facial emotion processing designs are used in order to ensure an identical task response across all conditions (M. L. Phillips et al., 1997). Participants can be asked to concentrate on a different aspect of the faces presented (e.g. to make a judgment about the gender or age) (Liu et al., 2012; M. L. Phillips et al., 1997). Especially in fMRI studies, the implicit design is often used to keep performances similar between groups (M. L. Phillips et al., 1997). Both designs have been reported to be associated with activation of the prefrontal cortex in healthy volunteers (Fusar-Poli et al., 2009). Explicit processing has shown a stronger association with activation in the amygdala, while implicit processing was stronger associated with activation in the inferior prefrontal cortex and insula (Fusar-Poli et al., 2009; Gorno-Tempini et al., 2001).

Patients with bipolar disorder and psychoses unrelated to childbirth have been found to show both deficits in facial emotion recognition performance and associated differences in brain activation as well as differential brain activation during implicit tasks (Bediou et al., 2005; Hoernagel et al., 2011; Kohler et al., 2010; Li et al., 2012; Malhi et al., 2007). However, bipolar patients appear to be more accurate than patients with psychoses unrelated to childbirth in recognising emotions (Rocca et al., 2009). In the following paragraphs, research findings will be discussed for both disorders separately.

6.1.1 Facial emotion processing in bipolar disorder

It is an established finding that patients with bipolar disorder show performance deficits in emotion recognition compared to healthy controls (V. Bozikas et al., 2007; Schaefer, Baumann, Rich, Luckenbaugh, & Zarate, 2010). It has been found that

processing negative facial expression such as fear seems to be associated with an underestimation of the intensity of the facial expression but with a more intense experience of the negative emotion (Hoertnagl et al., 2011; Rocca et al., 2009). Similarly to deficits in executive functioning found in bipolar disorder, facial emotion processing deficits seem to remain during euthymic phases (Hoertnagl et al., 2011). Some studies did not find evidence for trait like deficits in facial emotion processing in bipolar disorder and suggest that altered perception may rather indicate a mood-congruent bias (Gray et al., 2006; Venn et al., 2004).

Indeed, it has been reported that the extent of emotion recognition deficits varies according to the mood state, for example patients may display an enhanced recognition of fear during an acute manic state (Rocca et al., 2009), although a general trend towards an impairment in fear processing in bipolar disorder has also been highlighted by several authors (Lembke & Ketter, 2002; Rocca et al., 2009; Venn et al., 2004). Deficits in facial emotion processing seem to be independent of deficits in facial processing in bipolar disorder (V. P. Bozikas, Tonia, Fokas, Karavatos, & Kosmidis, 2006). Furthermore, there seems to be no association with gender, medication or symptom severity (Derntl, Seidel, Kryspin-Exner, Hasmann, & Dobmeier, 2009).

Impairments in facial emotion processing have been found to be accompanied by differences in brain activation in frontal, subcortical (specifically amygdala) and parietal activation compared to healthy controls (Lawrence et al., 2004; Lennox, Jacob, Calder, Lupson, & Bullmore, 2004; Malhi et al., 2007; Yurgelun-Todd et al., 2000). However, while the regions that show aberrant activation are quite consistent between studies, it has not yet been established, whether some regions are associated with a general decrease or increase of activation during facial emotion processing. Some studies reported reduced prefrontal, subcortical and parietal activation in bipolar patients compared to healthy controls (Malhi et al., 2007; van der Schot et al., 2010), while others demonstrated a limbic overactivation accompanied by a decreased prefrontal engagement (Delvecchio et al., 2012; Yurgelun-Todd et al., 2000). A reduced functional connectivity between the ventrolateral prefrontal cortex and the amygdala during an emotional task in bipolar disorder compared to healthy controls has also been reported (Foland et al., 2008). One explanation for the discrepancies in findings might be differences in task design such as the use of

implicit and explicit processing which have been associated with over- and underactivation in bipolar patients, respectively (C. Chen et al., 2006).

Due to the specific link to impaired recognition of fear, fMRI studies have often focused on the functional processing of fearful faces (Yurgelun-Todd et al., 2000). Typically reported are functional abnormalities in sub-cortical (i.e. amygdala) and ventral prefrontal regions for bipolar patients compared to healthy controls (Delvecchio et al., 2012; Lawrence et al., 2004; Yurgelun-Todd et al., 2000). This specific association has also been reported for psychoses unrelated to childbirth (Li et al., 2012; R. W. Morris, Weickert, & Loughland, 2009; Mukherjee et al., 2012).

6.1.2 Facial emotion processing in psychoses unrelated to childbirth

Patients with psychoses unrelated to childbirth show impaired performance in facial and other emotion recognition paradigms (Edwards et al., 2002; Schneider et al., 2006; Trémeau, 2006; Tsoi et al., 2008). There has been a claim that the deficit in facial emotion processing rather reflects a general deficit in facial processing linked to a reduced volume of the fusiform gyrus in psychoses unrelated to childbirth (Hooker & Park, 2002; Kohler, Bilker, Hagendoorn, Gur, & Gur, 2000; Onitsuka et al., 2006). Some studies also find overattribution of (negative) emotions to neutral faces (Eack et al., 2010; Habel et al., 2010). However, other studies do find a specific impairment in emotional processing, which seems to be most pronounced for negative emotions (Chan et al., 2010; Leppänen et al., 2006; Schneider et al., 2006). Furthermore, only facial emotion processing deficits seem to be correlated with positive and negative symptomatology and lead to problems in social interaction (Chan et al., 2010; Hooker & Park, 2002; Kohler et al., 2000; Poole et al., 2000). No correlations with length of illness or level of education have been reported (Leppänen et al., 2006). Facial emotion processing impairment has also been found in people at risk of psychosis (due to genetic risk or attenuated symptoms) and patients diagnosed with schizoaffective disorder, whereby “at risk” individuals and those diagnosed with schizoaffective disorder show intermediate levels to patients with psychoses unrelated to childbirth and healthy controls (Addington et al., 2008; G. P. Amminger et al., 2012; G.P. Amminger et al., 2012; Y. Chen et al., 2012; Leppänen et al., 2008; L. K. Phillips & Seidman, 2008).

Deficits in facial processing and facial emotion processing in psychoses unrelated to childbirth have been accompanied by aberrant brain activation (Habel et al., 2010; Li et al., 2012; Marwick & Hall, 2008; Reske et al., 2009). Similarly to bipolar disorder, there are some inconsistencies about whether specific areas can be associated with general decreases or increases in activation. Abnormal activation when processing emotional stimuli has been found in widely distributed areas such as the fusiform gyrus, amygdala, anterior cingulate, frontal areas, precentral and postcentral gyri, and temporal and parietal areas (Habel et al., 2010; Li et al., 2012; Marwick & Hall, 2008; Reske et al., 2009).

However, the frontal regions such the prefrontal cortex, the insula, anterior cingulate and orbitofrontal cortex and the amygdala seem to be of particular importance as these areas have been most consistently associated with dysfunctional emotional processing in psychoses unrelated to childbirth (Gur et al., 2002; Hempel, Hempel, Schönknecht, Stippich, & Schröder, 2003; Li, Chan, McAlonan, & Gong, 2010). This differential activation seems to be stable over time and not affected by symptomatology or length of illness (Li et al., 2010; Reske et al., 2007). According to the general consensus, patients with psychoses unrelated to childbirth are particularly impaired in recognising fear (Li et al., 2012; R. W. Morris et al., 2009; Mukherjee et al., 2012). The amygdala in particular has been ascribed an important role in fear processing, also in healthy individuals, and has been associated with reduced volume in psychoses unrelated to childbirth (Adolphs, 2008; Adolphs, Tranel, Damasio, & Damasio, 1995; Aleman & Kahn, 2005; J. S. Morris et al., 1996; Whalen et al., 1998). In several studies, aberrant amygdala activity to fearful faces has been reported in psychoses unrelated to childbirth alongside abnormalities in other areas including the frontal cortex (Das et al., 2007; Li et al., 2012; R. W. Morris et al., 2009). This was also reported for people at risk of psychosis with an intermediate activation between patients and healthy controls (Li et al., 2012). Furthermore, a reduced effective connectivity has been demonstrated between the amygdala and a large cluster of regions including the precuneus and parietal lobe in patients with psychoses unrelated to childbirth compared to healthy controls (Mukherjee et al., 2012). Also, there has been a report of no habituation of activation in the amygdala-hippocampal complex for fearful faces in patients with psychoses unrelated to childbirth compared to healthy controls, indicating that stimuli remain

salient (Holt et al., 2005). This suggests that the amygdala has a key role in understanding dysfunctional facial fear processing and we predict that it may also be dysfunctional in postpartum psychosis due to the close relationship to psychoses unrelated to childbirth.

In summary, facial emotion processing deficits are consistently reported in bipolar disorder and psychoses unrelated to childbirth with a pronounced impairment in fear processing. These deficits are associated with differential activity, most significantly in the amygdala when compared to healthy controls. Therefore, we expected to find a similar activation pattern in women at risk of postpartum psychosis when processing fearful faces. Specifically, we hypothesised that 1) women at risk of postpartum psychosis will show, in comparison to healthy controls, higher brain activation of the amygdala during a facial emotion processing task (primary hypothesis); 2) women at risk of postpartum psychosis will also show, in comparison to healthy controls, differential brain activation during the facial emotion processing task as assessed with whole brain analysis (secondary hypothesis); 3) differences in brain activation in facial emotion processing will be more pronounced in women who had developed postpartum psychosis episodes, compared to women who had not developed postpartum psychotic episodes, and to healthy controls (secondary hypothesis). In order to test this hypothesis, the Ekman faces task will be employed (chapter 6).

6.2 Methods

6.2.1 Participants, design, analyses and procedures

The methods have been described in chapter 2. For information on the combined group analyses and sub group analyses please see chapter 2 and chapter 3.

6.2.2 Ekman faces paradigm

An implicit Ekman faces paradigm was used, portraying fearful faces in order to assess emotional face processing while keeping performance levels similar across the groups (M. L. Phillips et al., 1997). Participants had to indicate the gender of 60 grey-scale images of five women and five men from the Pictures of Facial Affect series (Ekman & Friesen, 1976; M. L. Phillips et al., 1997) by pressing on either a

left (for female) or right (for male) button using a two button response box in the MRI scanner. Participants were not informed that the aim of the study was to investigate responses to emotional expression. Each face was presented six times, twice with a lower expression intensity of fear (50%) and twice with a standard expression of fear (100%) and two times with neutral expressions; see Figure 6.1. All participants received a training session prior to the MRI scan. During the training sessions neutral, lower, and standard expressions of happy were presented. The MRI task was presented in the form of an event-related design as 72 stimuli were randomly presented to participants, including 12 blank trials (i.e. a fixation cross). Images were displayed for two seconds followed by a fixation cross in the middle of the screen. The inter-trial interval was jittered (i.e. intervals were randomised between successive stimulus events) over a range between 3.33 and 8.64 seconds, with an average of 4.99 seconds. Paradigms were programmed using Visual Basic (VB.net) implemented on a PC running Windows XP Professional.

Figure 6.1 The Ekman faces task

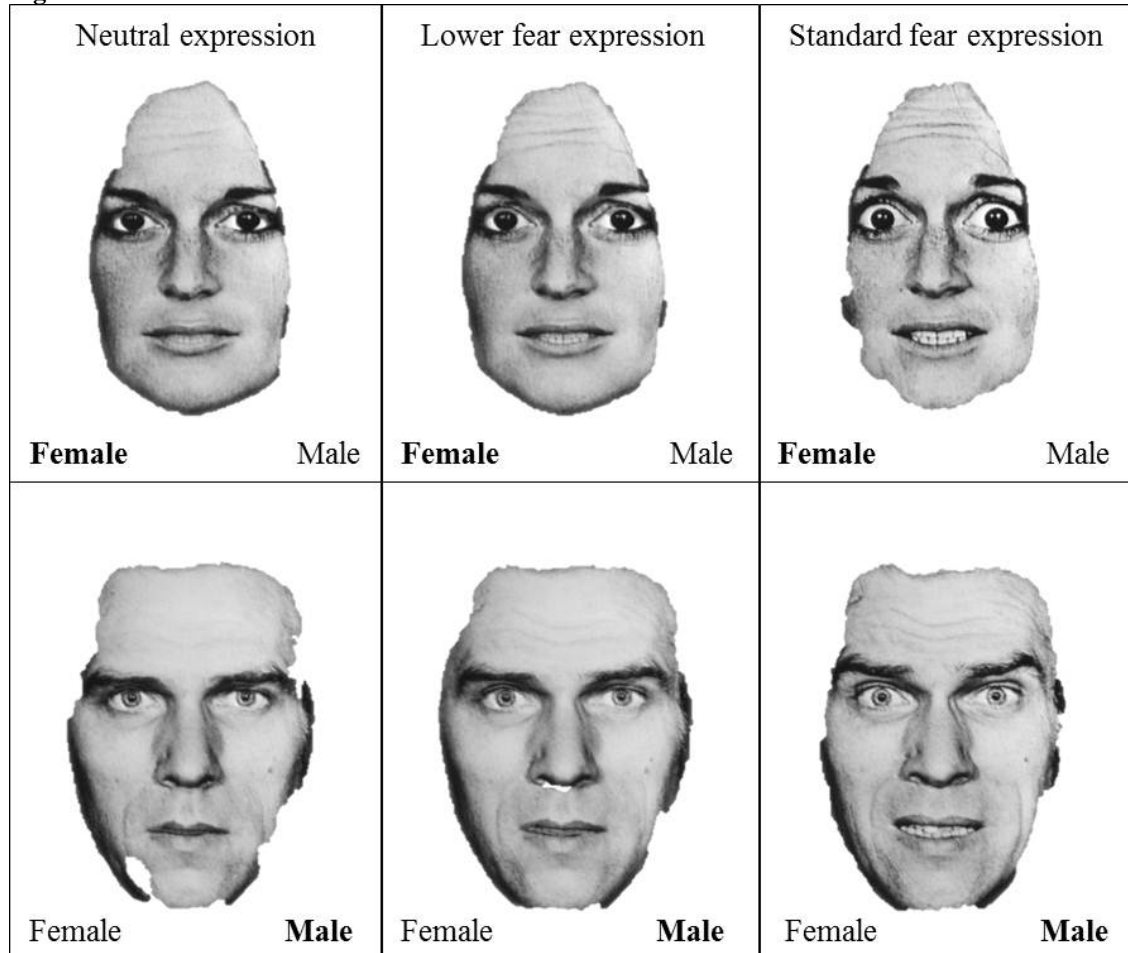


Figure 6.1 shows the female (first panel) and male (second panel) Ekman faces with ascending fear intensity. The first column shows neutral facial expression, the second column the lower intensity facial expression of fear and the last column the standard facial expression intensity of fear.

6.2.3 Analysis

For a further description of the behavioural and imaging analysis please see chapter 2. The dependent variables for the behavioural analysis were the number of correct responses (i.e. accuracy) for the neutral, lower and standard fear faces condition and the reaction times to all conditions. Specific contrasts of interest for the second-level model of the imaging analysis were the neutral, lower and standard fear faces versus an implicit baseline and the lower and standard fear faces (combined and separately) against neutral faces. We conducted a ROI analysis limited to the amygdala using the WFU PickAtlas tool in SPM. We also conducted a whole brain analysis. For a secondary analysis, in order to assess correlations with clinical variables, we also examined the contrast between lower and standard fear against neutral with a ROI analysis. The left inferior frontal gyrus was selected based on our results (MNI

coordinates $x=-34$, $y=16$, $z=28$). Spherical masks with a radius of 10mm were created around the coordinates using MARSBAR. Regions of interest were further analysed using SPSS 20 for Windows.

6.3 Results

Two healthy controls were excluded based on their behavioural performance. Both women had an error rate of more than 30% suggesting that they were not able to discriminate the gender of the faces. Another two women were excluded from the analysis because they had movement values greater than five mm/degrees. In total 42 women (NPE=12, PE=12, healthy controls=18) were analysed.

6.3.1 Performance results

No woman had a higher miss rate than 8% (i.e. four out of 60 faces) indicating that all remaining participants engaged in the task. The highest error rate of all three faces conditions combined was 23% (i.e. seven faces out of 60) after exclusion of the two outliers.

6.3.1.1 Combined group analysis

There were no significant accuracy differences between groups (“at risk” versus healthy controls) in the neutral, or standard fear faces condition ($z=-.05$, $p=.34$; $z=-.98$, $p=.33$). There was a significant difference between groups in the lower fear faces condition ($z=-2.03$, $p=.04$), with healthy controls performing better ($M=89$, $SD=4.16$) than the “at risk” group ($M=87$, $SD=5.28$). However, this represents a small difference of about 0.54 more faces recognised in the healthy controls, questioning the (clinical) relevance of this finding. Using a repeated measures between subject ANOVA, we found no significant interaction between group and reaction time (neutral, lower fear, standard fear) ($F(2,39)=.55$, $p=.58$) and no significant main effect of group ($F(1,40)=1.89$, $p=.18$); see Table 6.1 and Figures 6.2 and 6.4.

Table 6.1 Faces performance (CGA)

Groups	“at risk” M (SD)	healthy controls M (SD)
Accuracy (%)		
Neutral	86 (5.89)	88 (4.53)
Lower fear	87 (5.28)	89 (4.16)
Standard fear	88 (4.42)	89 (2.14)
RT		
Neutral	943 (176)	868 (128)
Lower fear	941 (167)	877 (147)
Standard fear	965 (161)	909 (141)

Table 6.1 shows the faces performance scores of the “at risk” group and healthy controls on accuracy and reaction time. RT=reaction time. M=mean. SD=standard deviation.

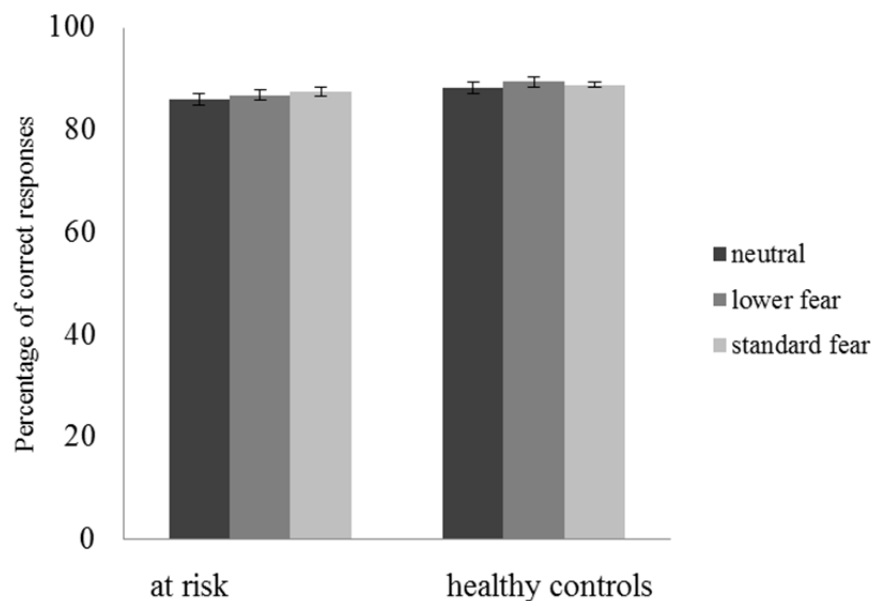
Figure 6.2 Faces performance - accuracy (CGA)

Figure 6.2 shows the mean faces task performance of the “at risk” group and healthy controls on accuracy. The y-axis shows the mean performance. The error bars show the standard error of mean (SEM).

6.3.1.2 Sub group analysis

There were no significant accuracy differences between groups (NPE, PE and healthy controls) in the neutral, lower or standard fear faces condition ($\chi^2(2,41)=1.49$, $p=.47$; $\chi^2(2,41)=5.01$, $p=.08$; $\chi^2(2,41)=1.16$, $p=.56$). There was also no significant interaction between group and reaction time (neutral, lower fear, standard fear) ($F(42,76)=1.12$, $p=.35$) using a repeated measures between subject ANOVA and no significant main effect of group on reaction time ($F(2,38)=1.59$, $p=.22$); see Table 6.2 and Figures 6.3 and 6.5.

Table 6.2 Faces performance (SGA)

Groups	NPE M (SD)	PE M (SD)	healthy controls M (SD)
Accuracy (%)			
Neutral	85 (5.82)	86 (6.36)	88 (4.53)
Lower fear	87 (5.82)	86 (5.05)	89 (4.16)
Standard fear	88 (3.99)	87 (5.18)	89 (2.14)
RT			
Neutral	928 (175)	983 (160)	868 (128)
Lower fear	931 (174)	975 (144)	877 (147)
Standard fear	969 (180)	982 (137)	909 (141)

Table 6.2 shows the faces performance scores of the NPE, PE and healthy control group on accuracy and reaction time. RT=reaction time. M=mean. SD=standard deviation.

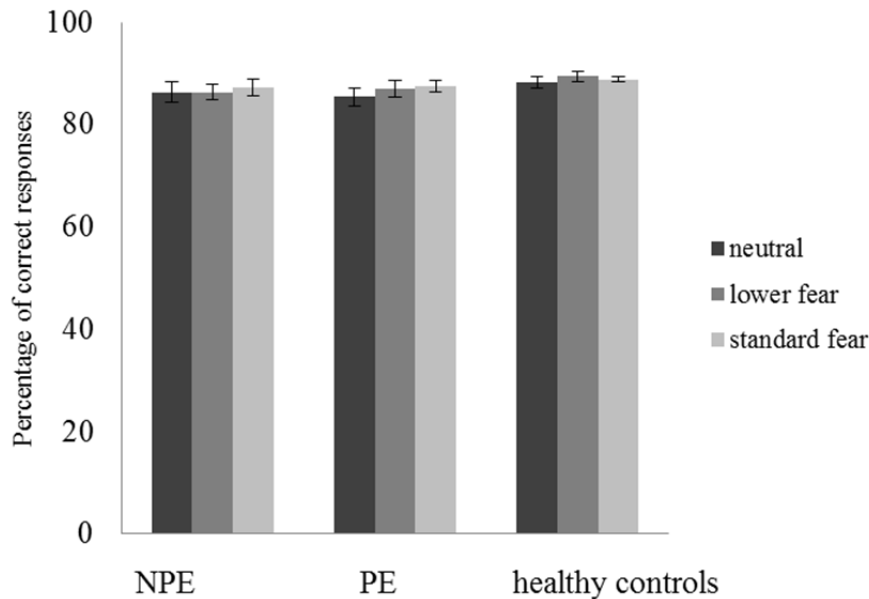
Figure 6.3 Faces performance - accuracy (SGA)

Figure 6.3 shows the mean faces task performance of the NPE, PE and healthy control groups on accuracy. The y-axis shows the mean performance. The error bars show the standard error of mean (SEM).

6.3.1.3 Intensity

There was no linear effect of accuracy across groups for the neutral, lower and standard fear faces condition ($\chi^2(2,42)=2.96$, $p=.23$). There was a significant linear main effect of RT with all participants responding slower to the standard fear faces conditions ($F(1,39)=6.28$, $p=.004$), with a significant difference between the lower and standard fear faces condition ($t(41)=-2.37$, $p=.02$) but not between the neutral and lower fear faces condition ($t(41)=-.24$, $p=.81$); see Figures 6.4 and 6.5.

Figure 6.4 Faces performance – reaction time (CGA)

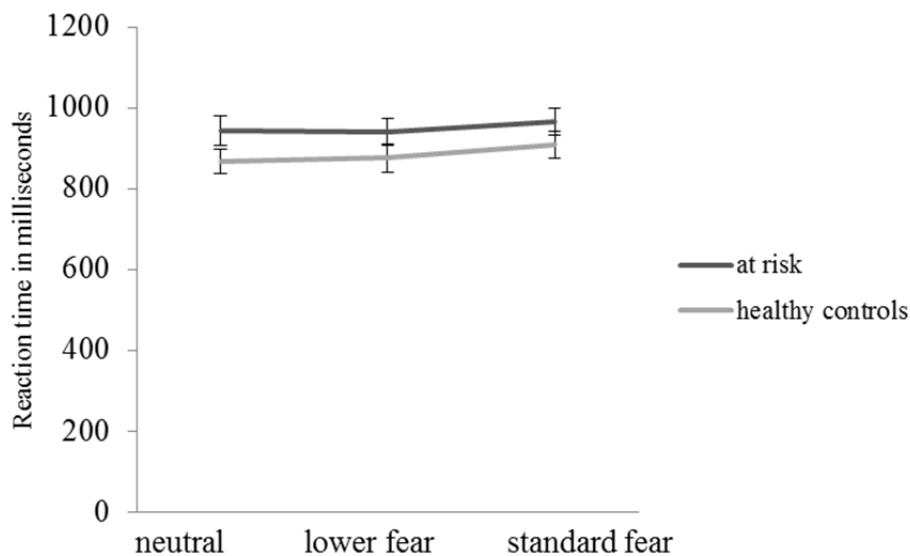


Figure 6.4 shows the mean reaction time of the “at risk” group and healthy controls during the three conditions of the Ekman faces task. The y-axis shows the mean reaction time. The error bars show the standard error of mean (SEM).

Figure 6.5 Faces performance - reaction time (SGA)

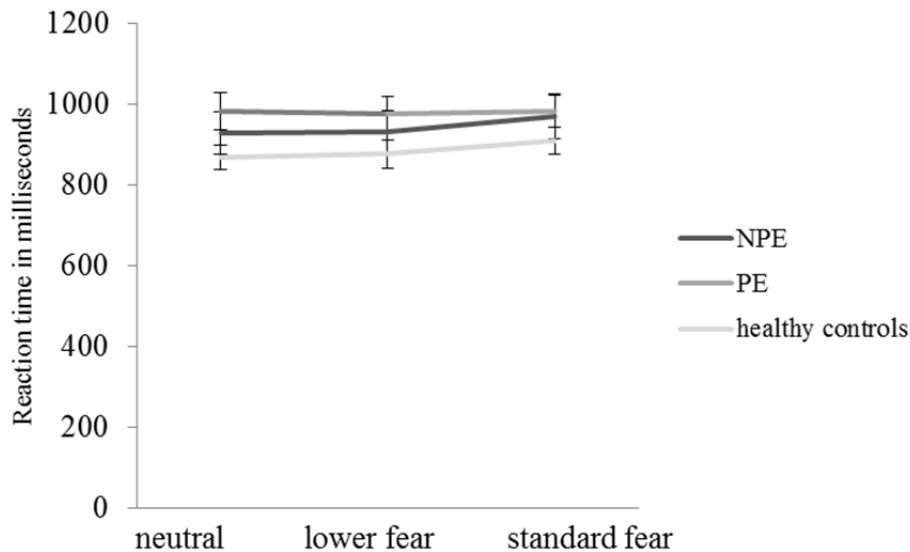


Figure 6.5 shows the mean reaction time of the NPE, PE and healthy control groups during the three conditions of the Ekman faces task. The y-axis shows the mean reaction time. The error bars show the standard error of mean (SEM).

6.3.1.4 Additional analyses

Based on the assumption, which was confirmed by our results, that the task is designed to produce equal performances across groups, we did not further investigate correlations between performances and clinical variables. As a further additional analysis we compared all women who were at risk of postpartum psychosis due to a

diagnosis of bipolar disorder (N=13) or other diagnoses (i.e. schizoaffective disorder, postpartum psychosis or family history) (N=11) and healthy controls (N=18). There was a non-significant difference between groups in the lower fear faces condition ($\chi^2(2,42)=5.98$, $p=.05$), with healthy controls performing better than the bipolar group ($z=-2.29$, $p=.06$, without Bonferroni correction). However, this represents a small difference of about 0.74 more faces recognised in the healthy controls, questioning the (clinical) relevance of this finding. There were no other performance differences between groups in accuracy or reaction time (smallest $p=.18$).

6.3.2 *Imaging results*

Two ROI analyses and two full-factorial models were conducted with 1) group (“at risk” versus healthy controls) as between subject factor and intensity (lower and standard fear against neutral) as within subject factor for the combined group analysis (2x2) 2) group (NPE, PE, and healthy controls) as between subject factor and intensity (lower and standard fear against neutral) as within subject factor for the sub group analysis (3x2). As a first analysis, we confirmed that the task robustly elicited the established faces task network in our participants including the fusiform gyrus, amygdala, frontal and temporal areas (Fusar-Poli et al., 2009). For that, we performed an analysis looking at brain regions activated by the neutral, lower, and standard fear conditions against the implicit baseline across all groups (CGA); see Table 6.3 and Figure 6.6.

Table 6.3 The faces task network for all faces conditions across groups

Area	x	y	z	BA	Voxels	Z	Pcor
R Inf Frontal	56	14	32	44	2685	>7.06	<.001
L Sup Medial Frontal	0	32	44	8	3	4.54	=.036
R Fusiform/Cerebellum	36	-38	-30	37	29915	>7.06	<.001
R Hippocampus/Amygdala	22	-22	-8	NA	3191	7.06	<.001
L Paracentral Lobule	-16	-24	78	4	1	4.69	=.043
R Supra Marginal	62	-16	22	48	113	5.33	=.001
L Mid Temporal	-48	-50	8	21	3	4.47	=.036

Table 6.3 shows the brain regions activated during the contrast “neutral, lower and standard fear>baseline”. X, y, and z refer to the MNI coordinates. BA refers to the Brodmann area and Z and Pcor give the Z value and the significant p-value (corrected for multiple comparisons on the basis of family wise error (FWE)). L refers to left and R to right side of the brain.

Figure 6.6 The faces task network for all faces conditions across groups

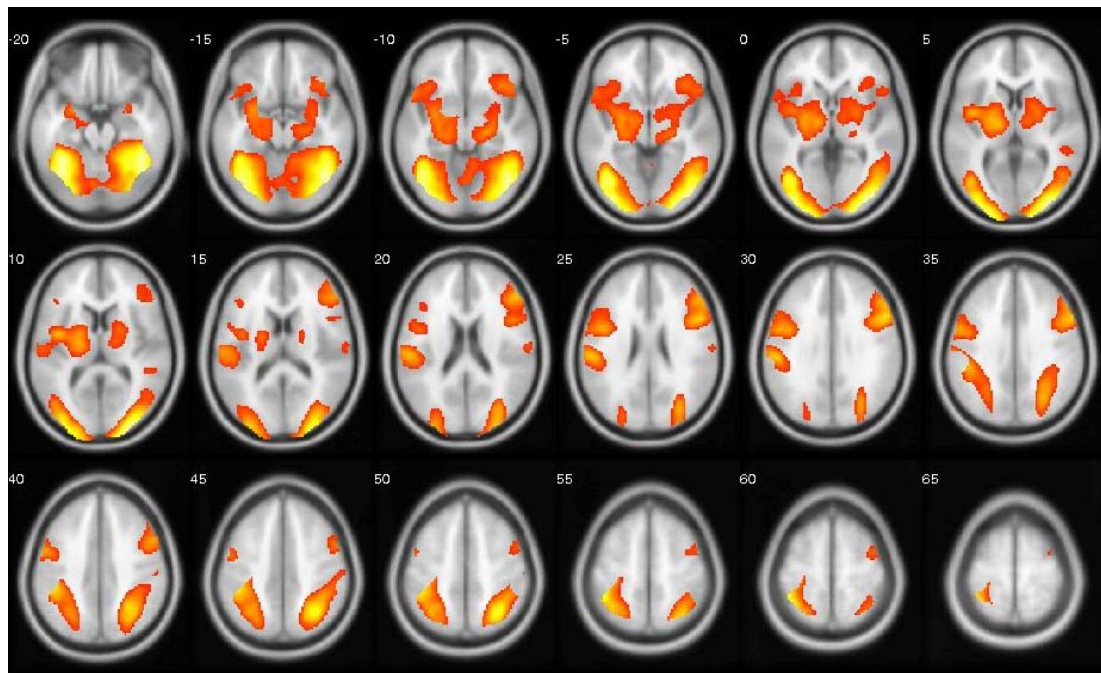


Figure 6.6 shows the brain regions activated during the contrast “neutral, lower and standard fear>baseline” overlaid on a high resolution T1-weighted template image in Montreal Neurological Institute space. Numbers refer to z coordinates. Voxels are corrected for multiple comparisons on the basis of family wise error (FWE). Left is the left and right the right side of the brain.

6.3.2.1 Fear intensity

We also investigated the effect of fear intensity across groups and found significantly higher activations in the frontal cortex, the fusiform gyrus, the postcentral gyrus and subcortical areas with increasing fear intensity in the 2x2 full-factorial model (CGA); see Table 6.4 and Figure 6.7.

Table 6.4 The faces task network for fear intensity across groups

Area	x	y	z	BA	Voxels	Z	Pcor
R Inf Frontal	42	8	26	44	363	6.39	<.001
L Inf Frontal	-38	6	26	48	36	4.85	=.009
R Inf Occipital/Fusiform	36	-68	-10	19	2963	6.89	<.001
L Mid Occipital/Fusiform	-38	-82	-2	19	2422	6.49	<.001
L Postcentral	-32	-30	54	3	61	6.17	=.004
R Thalamus	4	-6	-8	NA	52	4.69	=.005
L Thalamus	-8	-18	-10	NA	8	4.55	=.027
R Hippocampus	20	-20	-10	NA	6	4.51	=.030

Table 6.4 shows the brain regions activated during the contrast “standard fear>lower fear against neutral”. X, y, and z refer to the MNI coordinates. BA refers to the Brodmann area and Z and Pcor give the Z value and the significant p-value (corrected for multiple comparisons on the basis of family wise error (FWE)). L refers to left and R to right side of the brain.

Figure 6.7 Increase in fear intensity across groups

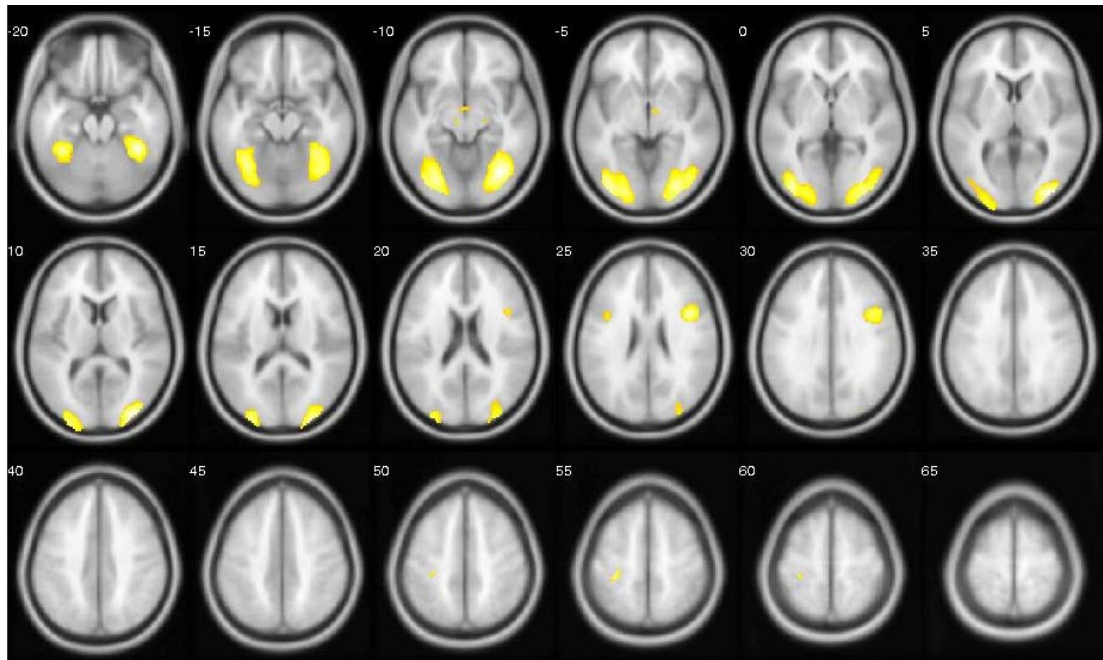


Figure 6.7 shows the brain regions activated during the contrast “standard fear>lower fear against neutral” overlaid on a high resolution T1-weighted template image in Montreal Neurological Institute space. Numbers refer to z coordinates. Voxels are corrected for multiple comparisons on the basis of family wise error (FWE). Left is the left and right the right side of the brain.

6.3.2.2 Group effects

There was no difference between groups following our ROI analyses. There were no interaction effects found between group (“at risk” versus healthy controls for the combined group analysis (2x2 factorial model) or NPE, PE and healthy controls for the sub group analysis (3x2 factorial model)) and fear intensity (standard fear>lower fear against neutral). There was also no significant group effect in the combined group analysis. However, we found a significant increase in the left inferior frontal gyrus in the PE group compared to healthy controls for the contrast of both fear conditions averaged against neutral; see Table 6.5 and Figures 6.8 and 6.9. There were no further significant differences in the sub group analysis.

Table 6.5 Group effect in the left inferior frontal gyrus, PE>healthy controls (SGA)

Area	x	y	z	BA	Voxels	Z	Pcor
L Inf Frontal	-34	16	28	48	390	4.01	=.050

Table 6.5 shows the brain regions activated during the contrast “standard fear and lower fear against neutral in PE>healthy controls”. X, y, and z refer to the MNI coordinates. BA refers to the Brodmann area and Z and Pcor give the Z value and the significant p-value (corrected for multiple comparisons on the basis of cluster extend .001). L refers to left and R to right side of the brain.

Figure 6.8 Group effect in the left inferior frontal gyrus, PE>healthy controls

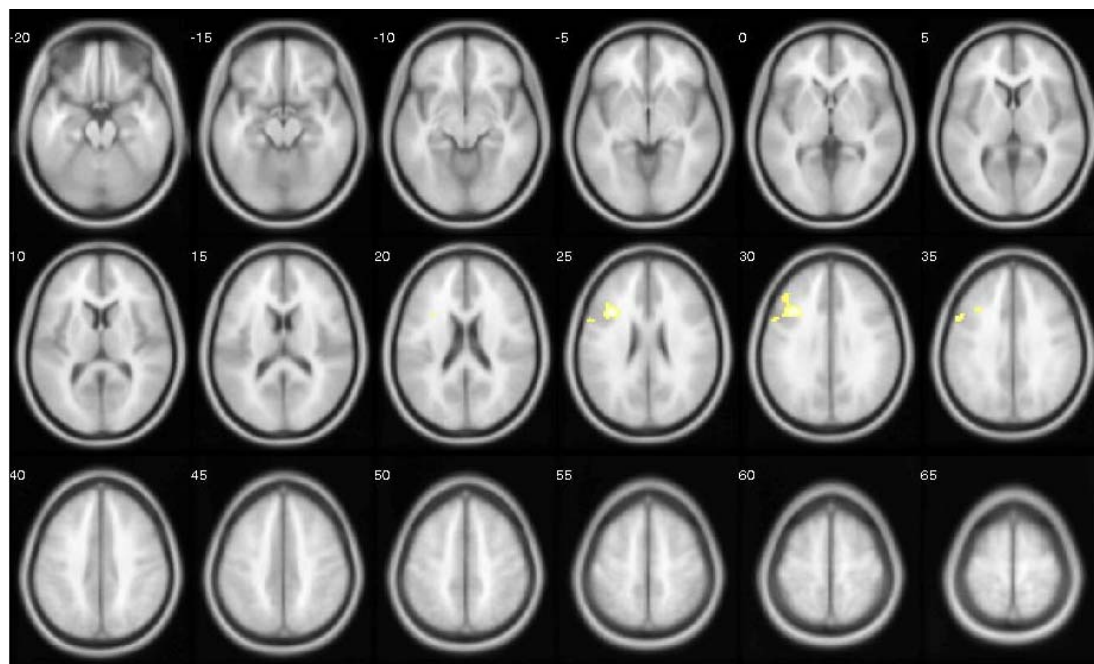


Figure 6.8 shows the brain regions activated during the contrast “standard fear and lower fear against neutral in PE>healthy controls” overlaid on a high resolution T1-weighted template image in Montreal Neurological Institute space. Numbers refer to z coordinates. Cluster are corrected for multiple comparisons on the basis of cluster extend ($P<.001$). Left is the left and right the right side of the brain.

Figure 6.9 Group effect in the left inferior frontal gyrus (SGA)

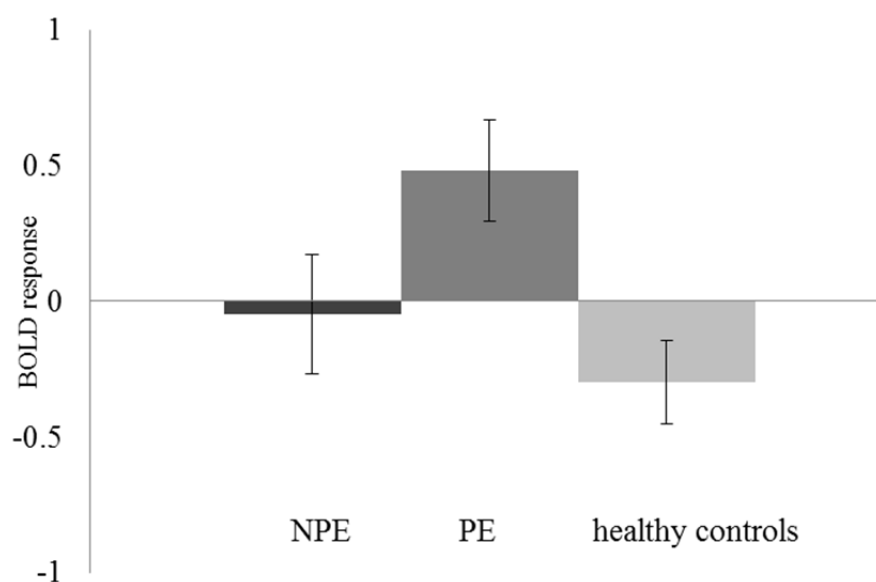


Figure 6.9 shows the significant increase of the PE group compared to healthy controls during the contrast “standard fear and lower fear against neutral” in the left inferior frontal gyrus (MNI coordinates: $x=-34$, $y=16$, $z=28$). The y-axis shows the mean BOLD response. The error bars show the standard error of mean (SEM).

The group effect was driven by a non-significant activation in the left inferior frontal gyrus areas by the PE group as assessed with a one sample t-test for the contrast standard fear>neutral (see Table 6.6).

Table 6.6 Activation in the PE group for the contrast all fear>neutral

Area	x	y	z	BA	Voxels	Z	Pcor
L Inf Frontal	-34	16	28	48	95	3.20	=.964

Table 6.6 shows the brain regions activated during the contrast “standard fear and lower fear against neutral” in the PE group. X, y, and z refer to the MNI coordinates. BA refers to the Brodmann area and Z and Pcor give the Z value and the significant p-value (corrected for multiple comparisons on the basis of cluster extent .005). L refers to left and R to right side of the brain.

6.3.2.3 Additional analyses

We did not find any supra-threshold clusters indicating group differences in the amygdala using the SPM WFU PickAtlas ROI approach. There were no significant correlations of the activation in the left inferior frontal gyrus with age, YMRS, HAM-D, PANSS, or length of illness (largest $r(23)=.29$, smallest $p=.17$). Antipsychotic medication (yes/no), age, scores of the YMRS, HAM-D, PANSS, or length of illness did not have significant effects on the imaging results when included as covariates in the full-factorial models. As a further additional analysis we compared all women who were at risk of postpartum psychosis due to a diagnosis of bipolar disorder (N=13) or other diagnoses (i.e. schizoaffective disorder, postpartum psychosis or family history) (N=11) and healthy controls (N=18). There were no significant group differences in activation when we compared all women diagnosed with bipolar disorder to healthy controls. However, when we compared women who were “at risk” due to other diagnoses, we found a significant increase in the left inferior frontal gyrus activation in this group compared to healthy controls, indicating that the previous result was mainly driven by women who were at risk of postpartum psychosis due to other diagnosis and women who have suffered a postpartum psychotic episode (see Table 6.7).

Table 6.7 Activation in the other “at risk” group for the contrast all fear>neutral

Area	x	y	z	BA	Voxels	Z	Pcor
L Inf Frontal	-34	16	28	48	1040	4.82	=.002

Table 6.7 shows the brain regions activated during the contrast “standard fear and lower fear against neutral” in the other “at risk” group compared to healthy controls. X, y, and z refer to the MNI coordinates. BA refers to the Brodmann area and Z and Pcor give the Z value and the significant p-value (corrected for multiple comparisons on the basis of cluster extent .001). L refers to left and R to right side of the brain.

6.4 Discussion

In this chapter, brain activation was investigated in women at risk of postpartum psychosis using the Ekman facial emotion paradigm portraying fearful faces. We expected that 1) women at risk of postpartum psychosis will show, in comparison to healthy controls, higher brain activation of the amygdala during a facial emotion processing task (primary hypothesis); 2) women at risk of postpartum psychosis will also show, in comparison to healthy controls, differential brain activation during the facial emotion processing task as assessed with whole brain analysis (secondary hypothesis); 3) differences in brain activation in facial emotion processing will be more pronounced in women who had developed postpartum psychosis episodes, compared to women who had not developed postpartum psychotic episodes, and to healthy controls (secondary hypothesis).

6.4.1 Summary of findings

As expected with an implicit facial emotion paradigm, there were no significant group performance differences in the combined or sub group analysis in accuracy or reaction times for the gender task. Contrary to our primary hypothesis, we did not find any increased activation in the amygdala of women at risk of postpartum psychosis. Still, we found a differential modulation in the form of a relative increase in activation in the left inferior frontal gyrus in the PE group compared to healthy controls when both fear conditions were compared to the neutral condition following the whole brain analysis. There were no significant correlations between activations and other variables such as clinical questionnaires, length of illness, age or medication. As the whole brain analysis was part of our secondary hypotheses, it may have been the case that our study was underpowered for this analysis.

6.4.2 Performance

As expected according to the implicit task paradigm used in this study, there were no significant group differences in the combined or sub group analysis in accuracy or reaction times for the gender task. All groups were slower in responding to fearful faces, which is in line with previous studies showing that responses to fearful faces or negative stimuli are slower than to happy faces or neutral stimuli (Blair et al., 2007; C. Chen et al., 2006). This further confirms that healthy controls and women “at risk” showed the expected behavioural variation with emotional faces and that the task worked in our population. Although the overall task accuracy was good (close to 90%), it was slightly lower than expected given that this study used a gender discrimination design (implicit emotion recognition). One reason for this could be the fact that women from various ethnic backgrounds took part in this study and may potentially have found it harder to rate some of the Caucasian faces used in the Ekman faces task. However, given that there were no differences between groups in ethnicity we do not expect this finding to have confounded the results. In addition, until now there are no consistent data on race effects for facial emotion paradigms (Kohler et al., 2010), suggesting that lower scores may have been caused by other factors such as the challenge of being in a scanner environment during the postpartum period while performing the task.

6.4.3 Imaging

We assessed the general facial emotion processing network across all groups, as in a previous meta-analysis it was found that controls and people with psychosis activate a qualitatively similar network during facial emotion task performance (Li et al., 2010). Our task elicited the expected network involved in facial and facial emotional processing including the inferior and superior frontal gyrus, fusiform gyrus, hippocampus and amygdala, paracentral lobule, and temporal areas (Fusar-Poli et al., 2009), indicating that the task manipulation worked. We furthermore found that there was an effect of fear intensity (i.e. standard fear > lower fear) across groups in the inferior frontal gyrus, fusiform gyrus, postcentral gyrus, and subcortical structures. This suggests that the groups responded as expected to the fear manipulation.

We did not find evidence to confirm our primary hypothesis. One reason for not finding differential activation within the amygdala as expected could be the use of an implicit task design. While both explicit and implicit task designs have been associated with frontal activation, the implicit task design showed a stronger modulation with the inferior frontal cortex and insula compared to a stronger amygdala modulation by explicit designs (Fusar-Poli et al., 2009; Gorno-Tempini et al., 2001). However, there are also other studies which do not find an aberrant activation in the amygdala in patients with psychoses unrelated to childbirth when compared to healthy controls (Holt et al., 2005; Li et al., 2012; Sachs et al., 2012; Surguladze et al., 2006). One possible explanation for this might be that our study and these other studies used neutral faces as a baseline which may reduce the capacity to detect abnormal amygdala activation (for a discussion see Li and colleagues (2012)) (Holt et al., 2005; Li et al., 2012). Alternatively, it has been suggested previously that altered emotion processing varies according to the mood state (Rocca et al., 2009) and may rather represent a mood-congruent bias than a trait like deficit (Gray et al., 2006; Venn et al., 2004). It could be that our group with non-postpartum episodes, which was euthymic at the time of the MRI scan, was not showing a current impairment in facial emotion processing, which may well become apparent during a potential relapse. Another explanation may be that our results show a gender effect, since it has been reported that males activate the amygdala more strongly during emotional processing (Fusar-Poli et al., 2009). However, others have reported that there is no effect of gender on facial emotion processing (Derntl et al., 2009). Finally, it may be that our study was not able to detect a difference between groups in amygdala activation due to fact that the effect size may was too small for the power of this study. Further studies and ultimately meta-analysis will be required to understand if this is the issue.

However, we found a relative increase in the frontal cortex, specifically in the left inferior frontal gyrus in the PE group compared to healthy controls for the contrast of both fear conditions averaged against neutral faces. The inferior frontal gyrus has previously been found to be implicated in emotional processing as well as in cognitive tasks in bipolar disorder and psychoses unrelated to childbirth (C. Chen et al., 2011; Gorno-Tempini et al., 2001; Li et al., 2012). Moreover, increased activation in the inferior frontal gyrus to fearful faces has been reported previously in

bipolar disorder compared to controls (Lawrence et al., 2004). While typically associated with response inhibition (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Aron, Robbins, & Poldrack, 2004; Rubia, Smith, Brammer, & Taylor, 2003), the increased activation may reflect a higher impulsivity or distractibility associated with bipolar disorder in the emotion regulation of women who had developed postpartum psychosis (C. Chen et al., 2011; Green, Cahill, & Malhi, 2007; Strakowski et al., 2010). However, we did not find any differences in reaction times, which would support this hypothesis.

The inferior frontal gyrus has also been found to show increased activation during fear processing in patients with panic disorder, which was reduced following cognitive behavioural therapy (Kircher et al., 2013). This suggests that women with postpartum psychosis may have had higher levels of fear (i.e. increased emotional responses) regulated by the inferior frontal gyrus while performing the task. In addition, the inferior frontal gyrus has also been involved in observation and imitation of facial expression, with an increase in activation during imitation when compared to observation only (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003). Taken together, if validated in larger studies, these results suggest that women who had developed postpartum psychosis showed a greater emotional response regulated by the inferior frontal gyrus, possibly due to feeling more empathetic and affected by the fearful faces.

6.4.4 Additional analyses

There were no correlations with other variables for the imaging results. This is in line with other studies of emotion processing as no association with length of illness, medication or symptom severity have been reported in bipolar disorder (Derntl et al., 2009; Leppänen et al., 2006). Only one study found a correlation between positive and negative symptomology and facial emotion processing deficits in psychoses unrelated to childbirth (Kohler et al., 2000).

6.4.4.1 Impact of bipolar disorder

We conducted an additional analysis in which women with a diagnosis of bipolar disorder were compared to women who were at risk of postpartum psychosis due to

other diagnoses and healthy controls. There were no significant performance or activation differences between the bipolar women and healthy controls or women “at risk” due to other diagnoses. However, women who were “at risk” due to other diagnoses showed a similar relative increase in activation in the left inferior frontal gyrus compared to healthy controls, as were found for the PE group. This suggests that the current results are mainly driven by the women who have suffered recently from postpartum psychosis and women who are at risk of postpartum psychosis due to other diagnoses rather than by a bipolar diagnosis. This possibly indicates a difference in emotional fear processing between euthymic women with a bipolar disorder diagnosis and women who have suffered from postpartum episodes and who are “at risk” due to other diagnoses.

6.4.5 Conclusion

In summary, women who had developed postpartum psychosis showed a relative increase in activation in the left inferior frontal gyrus compared to healthy controls which was not found in the non-postpartum group, suggesting an increased emotional response to the facial fear processing regulated by the inferior frontal gyrus. As the difference in the inferior frontal gyrus was part of the whole brain analyses, it will need to be validated in larger sample sizes in the future as it would not survive overall multiple comparison corrections ($P < 0.001$) of this study. In order to confirm our finding further support this hypothesis, future studies should also look at the physiological and reported fear response of women during and shortly after performing the task. It will also be of further interest to investigate functional connections of the inferior frontal gyrus and other regions during emotional fear processing in order to confirm a potential emotion regulation by the left inferior frontal gyrus.

7. Chapter: General discussion

In this chapter, an overview of the aims and hypotheses of this study will be given. This will be followed by a brief summary of the relevant findings and conclusions of each chapter. Then, a general discussion of the results and how they might relate to each other will be presented, followed by a discussion of the difficulties and limitations of this study. Finally, a potential future outlook and an overall conclusion will be given.

7.1 Overview of aims and hypotheses of the study

In the present study, one aim was to investigate potential clinical and sociodemographic correlates of postpartum psychosis and to make a tentative comparison to previous epidemiological studies. Furthermore, for the first time, it was assessed whether women at risk of postpartum psychosis have cognitive, emotional, or neuroimaging impairments similar to those reported in bipolar disorder and psychoses unrelated to childbirth. Specifically, we investigated whether:

Primary hypotheses:

1. Women at risk of postpartum psychosis will show, in comparison to healthy controls, decreased brain activation in the dorsolateral prefrontal cortex during a working memory task.
2. Women at risk of postpartum psychosis will show, in comparison to healthy controls, higher brain activation of the amygdala during a facial emotion processing task.

In addition, I will test a set of exploratory, secondary hypotheses:

1. Women at risk of postpartum psychosis will show, in comparison to healthy controls, differential brain activation during a working memory and facial emotion processing task as assessed with whole brain analysis.
2. Women at risk of postpartum psychosis will show, in comparison to healthy controls, impaired working memory performance.

3. Women at risk of postpartum psychosis will show, in comparison to healthy controls, impaired verbal memory performance.
4. Impairments in verbal and working memory and differences in brain activation in working memory as well as in facial emotion processing will be more pronounced in women who had developed postpartum psychosis episodes, compared to women who had not developed postpartum psychotic episodes, and to healthy controls.

7.2 Summary of findings

In the following section a general overview of the relevant findings and conclusions of each chapter will be presented, as the specific results have already been discussed in detail in the chapters. The multiple comparison issue will be discussed in section 7.5 Limitations, under 7.5.3 Power and multiple comparison correction.

7.2.1 Clinical and sociodemographic correlates

In the chapter assessing clinical and demographic correlates (chapter 3), we assessed whether women in the NPE, PE and healthy controls groups differed in their socioeconomic background, medical and obstetric history, medication or drug of abuse, or in life events, family history or clinical scales. Women were well matched for their socioeconomic background and medical and obstetric history. Medication use was also very similar between the postpartum and non-postpartum group in terms of type of medication and dose. There was no specific association between postpartum psychosis and life events, previous alcohol or illicit drug use or family history. However, there was an association between these variables and both “at risk” groups, suggesting that stressful life events, alcohol or illicit drug use, or a first-degree family history of psychiatric illness are important contributors to the development of mood and psychotic disorders in general (J. Savitz et al., 2009; Schäfer & Fisher, 2011).

There was no difference between the postpartum and non-postpartum group on scales assessing general functioning, mood, positive and negative symptoms, anxiety and stress. In addition, scores for positive and negative psychotic symptoms were low in both groups. This indicates that women in the PE group were relatively well at

the time of the MRI scan, although most of them had suffered a recent episode of postpartum psychosis. However, the mood, anxiety and stress scores still suggest that both groups may need additional support within the first year after childbirth independently of having suffered from a postpartum episode or not. In conclusion, the results of the clinical and sociodemographic correlates chapter suggest that women with postpartum psychosis presented similarly in their clinical profile to women with a diagnosis of an affective illness unrelated to childbirth. This is in line with previous studies suggesting no noticeable differences concerning the symptomatology between postpartum and non-postpartum episodes (Brockington et al., 1981; Reich & Winokur, 1970).

7.2.2 Verbal memory

To the best of our knowledge, this is the first time that verbal memory function has been assessed in women at risk of postpartum psychosis (chapter 4). We used a standardised assessment of verbal memory (i.e. logical memory I and II of the WMS-III) and an experimental verbal memory test using a remember-know paradigm. Significant impairments in the immediate recall as well as in recollection and familiarity were found in women at risk of postpartum psychosis in line with our secondary hypotheses. Women with postpartum and non-postpartum episodes showed a similar impaired performance compared to healthy controls, indicating that women with postpartum psychosis have a comparable verbal memory dysfunction to that observed in bipolar disorder and psychoses unrelated to childbirth (Aleman et al., 1999; Arts et al., 2008; Libby et al., 2012; Reichenberg, 2010; Reichenberg et al., 2009; L. J. Robinson et al., 2006). In addition, this difference emerged in two different tasks in a relatively small sample of women, suggesting that this is a robust finding and should be a key area in future research.

7.2.3 Working memory

As a second assessment of cognitive functioning in women at risk of postpartum psychosis, an fMRI working memory paradigm was employed (chapter 5). As expected in our secondary hypothesis, women at risk of postpartum psychosis showed a trend towards impaired task performance during the most challenging task

condition. The most pronounced difference in performance was observed in the non-postpartum group suggesting that women in this group employed a different strategy compared to healthy controls and women with postpartum episodes. Although our primary hypothesis was not confirmed, this difference in performance was also accompanied by a relative increase in activation in the non-postpartum group in the left midcingulate cortex and the bilateral superior temporal cortex following whole brain analysis. However, women who had suffered from postpartum psychosis showed a non-significant relative increase in activation in similar brain areas with intermediate activation levels compared to the NPE and healthy control groups. This differential activation possibly reflects an increase in the task demands, which may have been more challenging for the “at risk” groups due to a dysfunction in promoting task efficiency, resulting in a strategy change in this group. Furthermore, the activation profiles in both “at risk” groups indicate that women who have suffered from postpartum episodes show similar working memory deficits compared to women with non-postpartum episodes, bipolar disorder and psychoses unrelated to childbirth in general (Bora et al., 2010; I.N. Ferrier et al., 1999; Libby et al., 2012; Mur et al., 2007; L. J. Robinson et al., 2006; J. B. Savitz et al., 2008; Torres et al., 2007; Valli et al., 2012).

7.2.4 Facial emotion processing

In addition to assessing cognitive functioning in women at risk of postpartum psychosis, facial emotional processing was also investigated (chapter 6), as it is proposed to be one of the key impairments in bipolar disorder and psychoses unrelated to childbirth (Bediou et al., 2005; Brüne, 2005; Y. Chen et al., 2012; Hoernagl et al., 2011; Kohler et al., 2010; Malhi et al., 2007; Rocca et al., 2009). Our primary hypothesis was not confirmed. However, we found a differential modulation for fearful faces in the form of a relative increase in activation in the left inferior frontal gyrus in women with postpartum episodes compared to healthy controls. This finding suggests an increased emotional response to facial fear processing regulated by the inferior frontal gyrus. This modulation was not found between women suffering from non-postpartum episodes and healthy controls.

7.3 Overall discussion and implications of findings

Postpartum psychosis is a severe incapacitating illness with serious consequences for the mother and baby, such as a higher risk of suicide of the mother (Appleby et al., 1998; Babu et al., 2008; Brockington, 1996; Rohde & Marneros, 1993), risks of unsafe practices towards the baby (Chandra et al., 2006), and a high risk of a lack of emotional bonding or even separation between the mother and the child (Sit et al., 2006). However, evidence has shown that, when given appropriate care, the impact of postpartum psychosis on a child's development can be reduced (Murray et al., 2003). Therefore, it is of great importance to further develop our understanding of postpartum psychosis in terms of its cognitive and emotional correlates. These represent not only key aspects of normal daily functioning (e.g. independent living, work functioning and social interactions), but also central impairments reported in bipolar disorder and psychoses unrelated to childbirth and therefore are potentially of relevance in postpartum psychosis (Bediou et al., 2005; Bora et al., 2010; Bowie & Harvey, 2005; Brüne, 2005; Y. Chen et al., 2012; Hoertnagl et al., 2011; Kohler et al., 2010; Libby et al., 2012; Malhi et al., 2007; Mur et al., 2007; L. J. Robinson et al., 2006; Rocca et al., 2009; J. B. Savitz et al., 2008; Valli et al., 2012). Most studies conducted in women at risk of or suffering from postpartum psychosis have concentrated on clinical presentation, prognosis, and treatment of the disorder. Therefore, this thesis has helped to add data to an under researched area.

This is the first study to show that women at risk of postpartum psychosis present with deficits in verbal and working memory and facial emotional processing accompanied by differential brain activation compared to healthy controls, while being matched for sociodemographic, medical and obstetric and clinical variables. Although this pilot study may have been -considering a strict multiple comparison correction- underpowered, it may lead towards important implications. Women who have suffered from postpartum psychosis also show, in addition to a similar clinical profile, similarities in their cognitive profile to women with non-postpartum episodes, bipolar disorder and psychoses unrelated to childbirth in general (Bediou et al., 2005; Bora et al., 2010; Bowie & Harvey, 2005; Brüne, 2005; Y. Chen et al., 2012; Hoertnagl et al., 2011; Kohler et al., 2010; Libby et al., 2012; Malhi et al., 2007; Mur et al., 2007; L. J. Robinson et al., 2006; Rocca et al., 2009; J. B. Savitz et al., 2008; Valli et al., 2012). This finding is of significance, as, if extended in to

larger groups, it indicates that women with postpartum psychosis might be rightly placed into the diagnostic category of mood disorders representing a sub group of this nosological group. Furthermore, this may be especially interesting considering the recent debate on the new diagnostic criteria for postpartum mood disorders in the DSM-V, for which leading experts in the field (Jones & Smith, 2009) have recommended that postpartum psychosis is part of the usual categories and does not form a separate specific nosological entity. Considering our results, this conclusion can be supported.

Adding assessments of cognitive functioning, including tests of verbal memory and working memory, and neuroimaging measures to the clinical diagnostic criteria may help to provide a better understanding of the pathophysiology of this disorder. This may also lead towards better diagnostic tools for clinicians in recognising and diagnosing the disorder. Moreover, a more precise knowledge of potential underlying cognitive impairments may also be beneficial to the mothers, as targeted training programmes can be developed focusing on the cognitive recovery needs of patients.

Women who have suffered from postpartum psychosis show abnormalities in the emotional processing of fear, which is not found in women with non-postpartum episodes only. This indicates that there is potentially a difference between women presenting with postpartum and non-postpartum episodes, although this difference was not found in a direct contrast but in comparison to healthy controls. Nonetheless, differences in the facial emotional processing of fear may present an important characteristic associated with postpartum episodes. Facial emotional processing is important for social interactions, especially when the mother is interacting with an infant that is unable to express herself/himself. This should therefore be further explored in future studies with larger sample sizes.

7.4 Original study design and difficulties of the study

One contributing factor to the lack of research in postpartum psychosis is represented by the practical difficulties of conducting rigorous research in this group. This was also the case in this study, in which a difficult aspect was the practical set up, including the recruitment and data collection. As no previous study had looked at cognitive, emotional and neuroimaging correlates of women at risk of postpartum

psychosis around the time of delivery, a proposal was originally developed for an ambitious study with a prospective design. This protocol initially envisaged six study visits, including two antenatal visits around the 25th week of pregnancy and four postnatal assessments (two within the first week after delivery, also comprising the MRI scan), one eight weeks after delivery and a final one, one year after delivery. During these study visits the aim was to conduct clinical, cognitive and hormonal assessments of the mother, and of the mother and the baby after delivery. For an overview of the original study design up until eight weeks after delivery see Appendix E.

However, since it was anticipated that the original study protocol could be very challenging for women at the end of a pregnancy and after a delivery, we also planned for an alternate, less intensive protocol (described in chapter 2, Methods in the paragraphs 2.2 Design and 2.6 Procedure. For an overview see also Figure 2.11 Overview of all study assessments). Following several pilot runs conducted over the first 10 months of the study, it became clear that indeed the original study design was not feasible with the current study team. The reasons for this were:

1. Most women were physically too unwell after labour and delivery to travel to the Centre for Neuroimaging Sciences within one week after delivery.
2. Healthy controls and patients found it too challenging to undergo a study visit lasting approximately five hours, which included a 90 minute MRI scan, when they had a newly born baby.
3. Women who developed postpartum psychosis were also often mentally too unwell to be able to complete the assessments so close to delivery.
4. Many women who were first time mothers were reluctant to participate in the study as they felt they were not able to commit to the time it would take up in general.
5. During the first year of the study we recruited from only two sites including the King's College Hospital and the Royal Bethlem Mother and Baby Unit. This led to the identification of a relatively low number of potential participants that could be approached in the first place, given that postpartum psychosis is estimated to occur with an incidence of 1-2/1000.

These reasons also contributed to difficulties in assessing all women at around the same time point after delivery. This was especially true for the women who experienced a postpartum episode during the time of the study, since they often remained unwell for several months and could not be approached. As we had expected that certain changes had to be made to the protocol, a plan for review was in place 12 months into the study. Therefore, the study protocol was changed in the second year of the study without the need for ethics amendments.

The following changes were made to the protocol in December 2010:

1. The number of visits was reduced to two visits within the first year after delivery, in order to decrease the time commitment of the women taking part and increase the flexibility for assessments.
2. The time gap for the assessments after delivery was increased to up to one year, so that we could include women who had been severely ill after delivery and we could give all women more flexibility in terms of their time commitment.
3. Three additional study sites were added for recruitment, expanding the pool of potential participants.
4. The MRI scanning protocol was changed so that women could stop the scan after 60 minutes or 90 minutes depending on their well-being.

For an overview of the protocol see also chapter 2, Methods, paragraphs 2.2 Design and 2.6 Procedure and Figure 2.11 Overview of all study assessments. After these changes had been implemented, a sufficient number of participants were willing to take part and to complete the study. Given the rarity of the condition, the difficulties in identifying patients, and the problems in recruiting them into the study, future work in this area should build on these difficulties and be better designed in the context of multisite collaborations, which would result in well powered studies.

7.5 Limitations

As in other studies investigating disorders or diseases with low prevalence rates, several aspects need to be mentioned when interpreting the results of this study. These will be discussed in the following section.

7.5.1 Heterogeneity and the impact of bipolar disorder

A limitation of this study is the relatively small sample size of the sub groups. Our sample was quite heterogeneous, making it difficult to match the sub groups on different aspects such as diagnosis and postpartum episodes. For example, it was not possible to separate out women who had experienced both postpartum and non-postpartum episodes in order to create three sub groups. This would have been an interesting independent comparison to assess the effects of bipolarity on postpartum psychosis. However, based on the postpartum psychosis literature, categorising women into women with non-postpartum and women with postpartum episodes is considered a valid approach for analysis (P. Agrawal et al., 1990; Dean & Kendell, 1981; Dean et al., 1989; C. L. Katona, 1982; Kirpinar et al., 1999; Kisa et al., 2007; Platz & Kendell, 1988).

To try and disentangle the possible role of diagnosis, we repeated most comparisons with women categorised into those “at risk” due to a bipolar disorder diagnosis and those “at risk” because of other diagnoses, including most women with a recent postpartum episode. Results of these comparisons show that while women with bipolar disorder show the most severe cognitive impairments and differences in brain activation in working memory, women who are “at risk” because of diagnoses other than bipolar show an intermediate performance and activation profile. While these results may add little to the existing literature on bipolar disorder, they advance existing knowledge by indicating that women “at risk” of postpartum psychosis for other diagnoses still show impairments similar to those of patients diagnosed with bipolar disorder. More importantly, they suggest that women who have suffered from postpartum psychosis show similar cognitive impairments to patients with bipolar disorder unrelated to childbirth. Interestingly, facial emotion processing dysfunction was only reported in the postpartum episodes group and not in the bipolar group, indicating a possible difference between euthymic women with bipolar disorder and women who are “at risk” due to a previous episode or other diagnoses. If future studies have access to a larger pool of participants, the homogeneity of the sample for potential sub group comparisons would allow further clarification of these differences.

Another possibility would be to only look at risk factors for postpartum psychosis different from a history of bipolar disorder. However, as bipolar disorder is so highly

predictive of postpartum psychosis, it does not seem sensible to not take the most important risk factor into account. Some of the neurobehavioural correlates of this disorder may well be the very factors that are associated with the development of postpartum episodes. This is an aspect that deserves further clarification since not all women with bipolar disorder go on to develop postpartum psychosis after delivery. In order to be able to separate out the contributions of bipolar disorder in the future, it will be important to use a longitudinal approach and also look into more detail into the genetic contributions to postpartum psychosis.

7.5.2 *Healthy controls*

Healthy controls recruited into the study were matched to the “at risk” group on the following criteria: IQ, ethnicity, education and the number of weeks after delivery. In order to ensure that healthy controls did not differ on important socioeconomic variables, healthy women were recruited in the same hospital and from the same, relatively deprived, area in London as were women in the “at risk” group. In addition to that, we also applied the same inclusion/exclusion criteria to patients and controls, to limit the possibility that we included “well controls”, an approach which has been recently criticised in the literature (Schwartz & Susser, 2011). Only healthy controls with a current psychiatric diagnosis or one that was applicable to our “at risk” group were excluded.

Statistically, there were no significant or even trend differences in any of the above variables between the healthy control and the “at risk” group, implying that women were well matched regarding their socioeconomic background, medical and obstetric history in the current study. Still, as described in chapter 3, paragraph 3.4.7 Representativeness of the “at risk” group and healthy controls, healthy controls still had numerically a higher IQ, a higher employment rate and a higher rate of women with a degree or diploma. Importantly, there was also a tendency of healthy controls to have a higher age than the “at risk” group. Therefore, we cannot exclude that healthy controls and women in the “at risk” group differed on other important variables in addition to the ones we have assessed in the experimental chapters. For example, we cannot exclude that healthy controls showed a -better than normal- performance on the cognitive tasks and therefore that these could explain some of the differences we observed between groups. However, it is of note that our patients

group had a higher proportion of women in employment, especially in comparison to the local area (86%), and that these women were slightly above what is considered an average IQ (101.7), and therefore we have no reason to assume that their performance would be below the normal range. Furthermore, a comparison with other studies also suggests that the performance of the healthy women included in our study was within the normal range (Bell, 2006; Kieseppa et al., 2005).

Still we cannot exclude that this limitation may have, nonetheless, impacted on our results and it is of utmost importance in the future, to ensure that an healthy control group is even better matched on socioeconomic background and medical and obstetric history, so that a stringent comparison can be made between the “at risk” and the healthy control groups. Also for this reason a multisite collaboration would be preferable for the future of this study.

7.5.3 Power and multiple comparison correction

Important limitations in this study are the issues of power and multiple comparison correction. According to our calculations we had sufficient power for our primary hypotheses. However, the sample size was still relatively small. Especially for the second primary hypothesis, there was a lower predicted power. It is important to keep this limitation in mind when interpreting our study results. These will need to be confirmed by larger, better-powered studies in the future, in order to draw valid conclusions.

After delineating the primary hypotheses of the study, an overall multiple comparison correction was applied to the analyses of the explorative secondary hypotheses. We have calculated more than 50 comparisons, leading to a significance value set at $p=.001$ according to the Bonferroni correction. To adjust for such a high significance value, while formally controlling for Type I errors, potentially increases the likelihood of a Type II error. The power of the study becomes also more problematic when considering the issue of multiple comparisons as with a higher set significance value at $p<.001$, as more participants are needed in order to achieve the same statistical power. Due to the novelty of this work we cannot necessarily conclude that the groups do not differ in cognitive and emotional processing and differences found in this study may also identify potential important confounders, which can be taken into account in future studies. Furthermore, the conclusions

drawn from this pilot study are of great benefit for future studies in women at risk of or suffering from postpartum psychosis. This study has many practical implications for the setup and also suggests that women at risk of postpartum psychosis, including women with postpartum and non-postpartum episodes, show verbal and working memory and facial emotion processing impairments, which are important to be further investigated.

7.5.4 *Limitations of fMRI*

Since it is non-invasive, fMRI has become a very popular method in assessing brain function and the neurobiological correlates of neurocognitive and other psychological processes. As any other non-direct method, fMRI faces limitations that need to be considered when results of an imaging study are interpreted. For example, there are certain issues as to what deactivations or increases in brain activation actually mean in relation to cognitive processes (Logothetis, 2008). One of the main points that has been criticised in the literature is that fMRI does not measure neuronal activity directly (Huettel et al., 2004; Logothetis, 2008). (For an overview of the physics behind fMRI please see chapter 2, 2.4 Neuroimaging, 2.4.1 Background of fMRI). Although the fact that the BOLD contrast reflects neuronal activity evoked by a stimulus has been established in previous research (Logothetis, 2002, 2003), it remains possible that differences found between groups may relate to differences in neurovascular coupling in psychiatric disorders (D'Esposito, Deouell, & Gazzaley, 2003). Furthermore, the fMRI signal can also be confounded by other factors, such as medication or alcohol and substance abuse, which could be either only or to a larger extent, consumed by participants of one group and not the other (D'Esposito et al., 2003). As our study may be limited by these confounding effects, there is a more detailed discussion about possible effects of medication, symptoms, alcohol and substance abuse, hormones and menstrual cycle effects, and time after delivery on our results in the next section.

7.5.5 *Confounding variables and sources of variability*

As shortly discussed in chapter 2: Methods, paragraph 2.5.3 Potential confounders and sources of variability, in order to interpret the results of this study, it is also

important to look at the potential implications of confounding variables. In the following section, the effect of medications, symptoms, history of alcohol and substance abuse, hormones and menstrual cycle, and time after delivery will be discussed.

7.5.5.1 Medications

As discussed in the individual chapters of this thesis, the role of medications on brain activation and performance was considered. However, we found no significant difference in dose or type of medication used in the two patient groups. However, as in many other studies in bipolar disorder and psychoses unrelated to childbirth, it is difficult to assess and control well for the potential effects of medications, because of the variable length of exposure, the variability in dose or the heterogeneity of exposure (C. Chen et al., 2011). For example, in this study it was not possible to get the exact information on length of exposure and dose of medication for all women. This was due to the fact that not all medical notes were accessible or complete, and that the women could not reliably remember when they had started their medication and the different dosages. Therefore, we could not calculate chlorpromazine equivalents for all women and this prevented the possibility of a direct quantitative comparison. Still, in order to account for medication effects, antipsychotic medication was taken into account in additional analyses as a dichotomous variable (yes/no). It is important to note the conversion to chlorpromazine equivalents has in itself been criticised (Rijcken, Monster, Brouwers, & de Jong-van den Berg, 2003). The two main criticisms of using chlorpromazine equivalents are that, firstly, the newer atypical antipsychotic have a different mode of action and affect several neurotransmitters compared to the mainly dopaminergic action of typical antipsychotics, questioning the comparability of the medications (Rijcken et al., 2003; Stahl, 2008). The second criticism concerns the fact that there are no well controlled studies regarding dosage and potency on which a standardised use of chlorpromazine equivalents could be based (Rijcken et al., 2003), questioning the validity and reliability of using chlorpromazine equivalents in order to control for medication.

Taking medications into account has been problematic for all studies in patients treated with psychotropic drugs, as it makes it difficult to separate disorder effects from medication effects. However, it is important to note that previous studies show that medications do not seem to play a significant role in cognitive dysfunction in bipolar disorder or psychoses unrelated to childbirth (C. Chen et al., 2011; Goswami et al., 2009; Manoach, 2003; M. L. Phillips, Travis, Fagiolini, & Kupfer, 2008; L. J. Robinson et al., 2006; J. B. Savitz et al., 2008; Scheuerecker et al., 2008). It has been shown that unmedicated bipolar patients display the same cognitive deficits as medicated bipolar patients (Goswami et al., 2009). Furthermore, literature reviews have shown that antipsychotics may have a limited impact on fMRI findings and often seem to have rather normalising effects on brain function, (Hafeman, Chang, Garrett, Sanders, & Phillips, 2012; M. L. Phillips et al., 2008). However, some studies have also found that certain antipsychotics and lithium may be associated with increased volume in specific subcortical brain areas (Hafeman et al., 2012; Navari & Dazzan, 2009). Of specific importance to this study is the evidence that both antipsychotics and lithium increase prefrontal cortical activity during cognitive tasks and reduce limbic activity during emotion processing in bipolar adults, making activity more similar to that observed in healthy individuals (M. L. Phillips et al., 2008). This implies that the effect of medication may obscure between-group differences, possibly leading to Type II errors (Hafeman et al., 2012; M. L. Phillips et al., 2008)

This suggests that our findings of cognitive and emotional processing impairments in women at risk of postpartum psychosis are not easily explained by medication differences. Nevertheless, we are aware that subtle differences in activation and performance potentially due to medication could not be fully controlled for with our assessment of medication exposure. Therefore, it is of great importance in the future of this study to develop a more sophisticated and detailed assessment of medication.

7.5.5.2 Symptoms

As discussed in the section 7.4. Original study design and difficulties of the study, it was not possible to assess women who developed postpartum psychosis while they

were unwell, as they were often not able to give informed consent. Also, women had to be well enough to follow the instructions of the task and sustain attention for a relatively a long time. Nevertheless, a higher symptom score on mood and psychotic symptoms scales was still found in the “at risk” group compared to healthy controls, and the potential role of these symptoms on the findings should be considered. It has been suggested that certain symptoms (e.g. persistent mood symptoms such as depression) are associated with more pronounced cognitive impairments in bipolar disorder as well as in psychoses unrelated to childbirth (Iosifescu, 2012). Specifically, verbal memory has been associated with both depressive and negative symptoms (Aleman et al., 1999; Brébion et al., 2001; Pelletier et al., 2005; Reichenberg, 2010; Thoma et al., 2006). Also, emotion recognition deficits have been found to vary with mood state, with depressed bipolar patients showing a mood congruent bias (a decreased sensitivity to happy faces and an increased sensitivity to sad faces) (Gray et al., 2006). In addition, facial emotion processing deficits seem to correlate with positive and negative symptomatology (Chan et al., 2010; Hooker & Park, 2002; Kohler et al., 2000; Poole et al., 2000). Still, it is also known in the literature that cognitive and facial emotion processing deficits persist during euthymic phases of patients with bipolar disorder (Hoertnagl et al., 2011; Townsend et al., 2010).

To control for the potential confounding effects of mood and psychotic symptoms is difficult, as they are so intrinsically linked to psychiatric disorders that controlling for symptoms actually may take away the “group effect” (Miller & Chapman, 2001). Nonetheless, in order to assess the effect of symptoms on the dependent variables in our study, we conducted correlations between the performance scores and activation and manic symptoms as assessed by the YMRS, depressive symptoms as assessed by the HAM-D, and positive or negative symptoms as assessed by the PANSS for each task. We did not find any correlations between clinical scales and performance or brain activation.

There were also no significant differences between the postpartum and the non-postpartum group on any symptom scales. There was a significant difference with healthy controls, but the results on the YMRS, the HAMD-D and the PANSS suggest that the “at risk” group as a whole had very low scores on the clinical scales. This indicates that women in both groups (postpartum and non-postpartum) were virtually euthymic at the time of the scan, as the low scores were below the least stringent

criteria for euthymia proposed in a review on cognitive deficits in euthymic patients with bipolar disorder (L. J. Robinson et al., 2006). These low scores on the clinical scales, as well as the lack of correlations between such scores in our study, suggests that mood and psychotic symptoms were not heavily confounding the results of this study. Still, as symptoms have been associated with cognitive impairment and facial emotion processing deficits in previous studies, it will be important to further investigate their potential influence in the future.

7.5.5.3 Alcohol and substance abuse

Alcohol and substance abuse can have a profound impact on brain structure as well as on brain functioning (Leshner & Koob, 1999; Oscar-Berman & Marinkovic, 2003; Schulte et al., 2012). It is established that heavy and chronic alcohol and other drug abuse can lead to lasting changes in the brain affecting cognition and emotional functioning (Benningfield & Cowan, 2013; Büttner, Mall, Penning, Sachs, & Weis, 2003; Schulte et al., 2012). Therefore, it is important in research studies to control for potential acute, but also lifetime, alcohol or drug abuse. Unfortunately, in psychiatric populations it is often difficult to recruit participants with no history of alcohol or substance abuse. Often rates of abuse are higher in psychiatric populations than in the control population, and bipolar disorder has been commonly associated with alcohol abuse (McDonald & Meyer, 2011).

None of the women in our sample reported any use of alcohol or other drugs of abuse during or after the pregnancy. However, 32% of women in the “at risk” group had a history of alcohol or substance abuse, while in the healthy control group none of the women reported any history of abuse. This result presents a potential confounder for the analysis. Due to the fact that we did not have a detailed assessment on history of abuse in addition to the SCID-I CV, we were not able to take history of alcohol or substance abuse into account in the analysis. Furthermore, the resulting low numbers would have made a statistical comparison difficult. However, as this was the first study conducted in women at risk of postpartum psychosis, it also has the purpose to identify potential confounders that are important to be controlled for in future research in this population. It will be important to adequately assess and control for acute and past alcohol and drug abuse by using

appropriate assessment tools, recruiting sufficient numbers of participants and also matching the healthy control group on this variable.

7.5.5.4 Hormones and menstrual cycle effects

One major limitation of this study is related to the difficulty to reliably assess differences in hormonal levels between women. The main reason for this was the large variation between women in the time of assessments after delivery. Although blood samples were taken in order to assess hormone levels, a comparison would have been difficult since some women had not had a first menstrual cycle after delivery while others did, and a few women were already on contraceptives. In the future, it will be of importance to streamline the assessments concerning the time after delivery as also discussed in paragraph 7.5.5.5 Time after delivery. This will help clarify whether hormonal changes that occur after delivery differ between groups and whether they affect the measures of interest (e.g. verbal memory, working memory).

As discussed in the introduction under paragraph 1.3.1.3 Menstrual cycle effects, assessing the current point in the menstrual cycle is also of great importance, as it may influence other biological parameters (e.g. cortisol levels, thyroid function) (Rubinow & Schmidt, 1995) as well as neurocognitive functions such as spatial working memory, selective attention and verbal memory (Craig et al., 2008; Craig et al., 2007; Hausmann et al., 2000; Maki et al., 2002; Man et al., 1999; Symonds et al., 2004; Thimm et al., 2013). We only considered “having had a menstrual cycle after the most recent delivery” as a dichotomous variable into the additional analyses, specifically of the verbal memory task and found that it did not affect the results. This of course does not replace a detailed assessment of menstrual cycle phase and of subtle differences in hormonal levels. Unfortunately, since most women did not have a regular cycle yet after delivery, it was not possible to assess the effect of cycle phase. Therefore, we cannot exclude that hormonal variations represent a confounder in the current analysis and possibly influence the performance as well as the neuroimaging parameters. It is essential in future studies to pay special attention to this issue in order to make meaningful and valid comparisons between groups and to explore the possible interaction between hormone levels and an underlying brain

vulnerability. One valuable approach to assess menstrual cycle history has been presented by Symonds and colleagues (2004), using the Calendar of Premenstrual Experience (CoPE) along with recording the length of menstruation, abnormal mid-cycle bleeding and length of cycle (Mortola, Girton, Beck, & Yen, 1990; Symonds et al., 2004). In summary, follow ups of this study, or future studies would hugely benefit from streamlining the time points of assessments after delivery as well as assessing the phase of the menstrual cycle.

7.5.5.5 Time after delivery

One of the most important reasons behind a change in the original study design was that women were not able, shortly after delivery, to undergo the MRI research visit. This applied to the healthy controls, but even more so to the women who developed a postpartum psychotic episode, as they often remained unwell for several months and could not be approached for research purposes. For this reason, the time period for recruitment was extended to up to one year after delivery. Unfortunately, this increased the variability in the number of weeks after delivery between participants. Although we controlled for weeks after delivery between groups, we cannot exclude that this variability had an impact on our results. For example, there could be a “carry-over” effect of pregnancy. Many women report a cognitive deterioration during pregnancy and early postpartum period and this is also partly supported by evidence from studies assessing cognitive function during pregnancy and early motherhood (De Groot, Vuurman, Hornstra, & Jolles, 2006; Henry & Rendell, 2007; Rendell & Henry, 2008). This would imply that women who have been assessed closer to the delivery may have performed worse than women who had more time to recover.

However, we believe this is unlikely. Firstly, weeks after delivery was taken into account in the cognitive tasks analyses and did not influence the results. Secondly, a recent study, and the first one done prospectively, highlights that, contrary to popular opinion, cognitive functioning does not seem to deteriorate during pregnancy, but may have been a result of sampling bias (Christensen, Leach, & Mackinnon, 2010). In addition, time after delivery was matched between groups and the time range was

restricted to one year after delivery, with the longest time interval being 43 weeks. This is a relatively short time-frame considering the complexity of the assessments.

Nonetheless, as discussed in the previous paragraph 7.5.5.4 Hormones and menstrual cycle effects, the variability in time after delivery made it impossible to assess the hormone levels in a structured way as some women had not had a first menstrual cycle after delivery while others did, and a few women were already on contraceptives. Also the differences in time after delivery led inevitably to some women having already stopped breastfeeding while other still did. This again is a factor that has a huge impact on hormonal levels and therefore also the potential to impact on brain functioning. Therefore, future studies may need to streamline the time points of assessments as much as practically possible.

7.6 Future outlook

The findings in this thesis represent a first important step towards a better understanding of cognitive, emotional and neuroimaging processes in women at risk of or suffering from postpartum psychosis. In order to further develop this knowledge, future analyses should implicate other biological correlates. Two interesting correlates are oestrogen and cortisol levels, the importance of which has been described in the main introduction of this thesis.

7.6.1 Cortisol

As discussed before, high cortisol levels are associated with stress and childbirth. In addition, higher cortisol has been found in patients suffering from mental health disorders such as depression and psychoses unrelated to childbirth (Aiello et al., 2012; Bennett & Maxwell, 2008; Hendrick et al., 1998; Schäfer & Fisher, 2011). One pilot study also reported higher cortisol levels in women who developed postpartum psychosis (Paykel et al., 1991). Therefore, it would be interesting to investigate possible differences in cortisol levels between women with non-postpartum and postpartum episodes and healthy controls. This would be particularly interesting considering that a higher percentage of women at risk of postpartum psychosis have a history of stressful or intrusive life events and report more physical and sexual childhood abuse compared to healthy controls. Furthermore, women in

both “at risk” groups experienced more subjective stress and higher anxiety at the time of the MRI scan and women who had suffered from postpartum psychosis showed differential brain activation to fearful faces. These results are indicative that a higher cortisol response may be present in women at risk of postpartum psychosis.

7.6.2 Structural imaging

Based on the results in this study, showing differences in functional brain activation in a working memory and a facial emotion processing task, it would be of further interest to investigate potential structural differences in both “at risk” groups. It has been previously reported that certain brain areas show an increased activation as a functional compensation for structural abnormalities (i.e. volumetric grey matter reductions) in first episode as well as chronic schizophrenia (Kuroki et al., 2006; Onitsuka et al., 2004). Therefore, investigating potential volumetric differences in our women at risk of postpartum psychosis may shed more light on the functional activation differences that were found.

In addition, an enlarged volume of the pituitary has been associated with being in a high-risk state of developing bipolar disorder and psychoses unrelated to childbirth (Aiello et al., 2012; Mondelli et al., 2008). This increase in the pituitary has furthermore been associated with higher cortisol levels and stress reactivity (Aiello et al., 2012). It would be interesting to assess cortisol levels and their potential association with an increased volumetric volume of the pituitary and higher levels of reported stress and anxiety.

Finally, another structural measure of interest would be the assessment of the white matter in women at risk of postpartum psychosis, as differences in white matter have been also associated with stress and childhood trauma (Daniels, Lamke, Gaebler, Walter, & Scheel, 2013). Intact myelin content is important for functional white matter connections (S. C. Deoni et al., 2008), which are in turn responsible for a good processing speed needed for cognitive functioning (S. C. L. Deoni, Dean Iii, O'Muircheartaigh, Dirks, & Jerskey, 2012). Therefore, it would be important to investigate potential alterations of myelin content and a possible association with cortisol levels in women at risk of postpartum psychosis.

7.6.3 Follow-up studies

Women were assessed retrospectively in this study in terms of number of episodes and length of illness. For this reason we cannot exclude that women in the non-postpartum group may develop postpartum episodes at a later time point. Likewise, women who experienced a first or second postpartum episode may develop non-postpartum episodes later on. It would be of great interest to follow these women up at a later time point in order to assess whether they have suffered from new episodes. A later follow-up visit including a second MRI scan may also clarify whether the impairments we found are stable over time or whether women show a decline in verbal or working memory function or in facial emotion processing. In addition, it would be also of interest for future studies to assess women already during the pregnancy and follow them up postpartum in order to assess potential risk factors predictive of postpartum psychosis.

Of further interest would be, in addition to the assessment of the mothers, the evaluation of the effects of a postpartum psychotic episode on the child in terms of their cognitive and emotional development. Another possibility would be to measure stress levels of the child using biological measures. Furthermore, recent advances in imaging research show that babies as young as several months can undergo MRI scanning in order to assess myelin content (S. C. L. Deoni et al., 2012). Since this seems a potentially important measure in the mother, it would be useful to see whether alterations can also be found in their offspring.

7.7 Final conclusion

The results of this study represent an important first step towards a better understanding of cognitive and emotional processes and associated brain activation patterns in women at risk of or suffering from postpartum psychosis. Identifying correlates in women “at risk” may represent an important aid for clinicians. For example, the presence of some of these factors may in the future help to identify the subset of women who are at a particularly high risk of developing a postpartum episode and therefore help in guiding preventative pharmacological interventions. In addition, more in-depth knowledge and understanding of these processes may help clinicians to develop targeted cognitive training and therapies in addition to the

pharmacological treatment available, potentially speeding up the recovery process in those women who have been affected by an episode.

8. References

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Appendix A

Wechsler Test of Adult Reading (WTAR)

- | | |
|------------------|-------------------|
| 1. Again | 26. Conscientious |
| 2. Address | 27. Homily |
| 3. Cough | 28. Malady |
| 4. Preview | 29. Subtle |
| 5. Although | 30. Fecund |
| 6. Most | 31. Palatable |
| 7. Excitement | 32. Menagerie |
| 8. Know | 33. Obfuscate |
| 9. Plumb | 34. Liaison |
| 10. Decorate | 35. Exigency |
| 11. Fierce | 36. Xenophobia |
| 12. Knead | 37. Ogre |
| 13. Aisle | 38. Scurrilous |
| 14. Vengeance | 39. Ethereal |
| 15. Prestigious | 40. Paradigm |
| 16. Wreathe | 41. Perspicuity |
| 17. Gnat | 42. Plethora |
| 18. Amphitheatre | 43. Lugubrious |
| 19. Lieu | 44. Treatise |
| 20. Grotesque | 45. Dilettante |
| 21. Iridescent | 46. Vertiginous |
| 22. Ballet | 47. Ubiquitous |
| 23. Equestrian | 48. Hyperbole |
| 24. Porpoise | 49. Insouciant |
| 25. Aesthetic | 50. Hegemony |

Brief life events questionnaire (BLE)

The following questions are about events or problems which may have happened to you during the past 6 months which might have caused you distress and to seek help.

1. In the last 6 months, did you suffer from a serious illness, injury or an assault?
If yes, at that time, how bad was that for you?
2. In the last 6 months, did a serious illness, injury or assault happen to a close relative?
If yes, at that time, how bad was that for you?
3. In the last 6 months, did a parent, spouse (or partner), child, brother or sister of yours die?
If yes, at that time, how bad was that for you?
4. In the last 6 months, did a close family friend or other relative die, such as an aunt, cousin or grandparent?
If yes, at that time, how bad was that for you?
5. In the last 6 months, did you have a separation due to marital difficulties or break off a steady relationship?
If yes, at that time, how bad was that for you?
6. In the last 6 months, did you have serious problems with a close friend, neighbour or relatives?
If yes, at that time, how bad was that for you?
7. In the last 6 months, were you made redundant or sacked from your job?
If yes, at that time, how bad was that for you?
8. In the last 6 months, were you seeking work without success for more than 1 month?
If yes, at that time, how bad was that for you?
9. In the last 6 months, did you have a major financial crisis such as losing the equivalent of three months' income?
If yes, at that time, how bad was that for you?
10. In the last 6 months, did you have problem with the police involving a court appearance?
If yes, at that time, how bad was that for you?
11. In the last 6 months, was something you valued lost or stolen?
If yes, at that time, how bad was that for you?
12. In the last 6 months, have you had any major pregnancy-related problems?
If yes, at that time, how bad was that for you?

Intrusive life events (ILE)

Instructions to researcher: Please ask participant the following - I would now like to ask you about things that may have happened to you or problems you may have faced throughout your life. Looking at the list above, can you tell me if you have ever suffered from any of the problems or events shown on the card, at any time in your life?

a) Serious injury or assault to yourself:

b) Bullying:

c) Violence at work:

d) Violence in the home

e) Sexual abuse

f) Being expelled from school

g) Running away from home

h) Being homeless

i) Taken into local authority care

j) Time in children's institution

Childhood experience of care and abuse questionnaire (Ceca-Q)

I'm going to ask you some questions about your childhood experiences. If you prefer not to answer any of the questions, that's fine – just say you'd rather not answer.

Who brought you up before age 17?

Family Arrangements (all)

Were you ever in a children's home or institution prior to age 17?

If yes, type of institution:

Parental Loss and Separation

Did either parent die before you were aged 17?

Have you ever been separated from either parent for 6 months or more before 17?

Physical Punishment before the Age of 17 by a Parent Figure or Other Household Member

When you were a child or a teenager were you ever hit repeatedly with an implement (such as a belt or stick) or punched, kicked or burnt by someone in the household?

b) How old were you when it began?

c) Did the hitting happen on more than one occasion?

d) How were you hit?

f) Were you ever injured, e.g. bruises, black eyes, broken limbs?

g) Was this person ever so angry they seemed out of control?

Please describe your experience (not for data entry)

h) Did you experience this from anyone else in the household?

Please describe your experience (not for data entry)

Unwanted Sexual Experiences before Age 17

When you were a child or teenager did you ever have any unwanted sexual experience

Did anyone force you or persuade you to have sexual intercourse against your wishes before age 17?

Can you think of any upsetting sexual experiences before age 17 with a related adult or someone in authority, e.g. teacher?

How old were you when it began?

ii) Was the other person someone you knew?

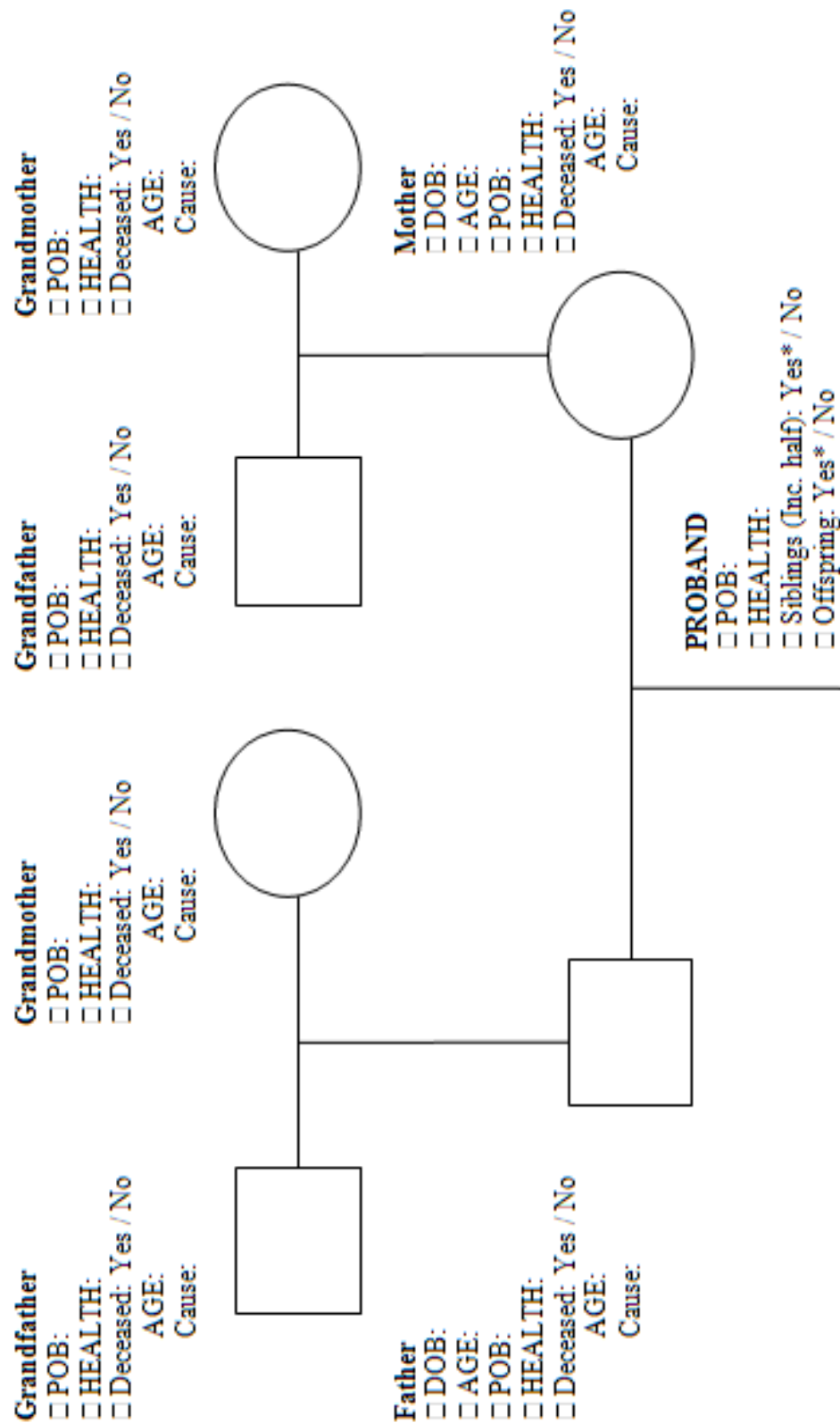
iii) Was the other person a relative?

iv) Did this person do it on more than one occasion?

v) Did it involve touching private parts of your body?

vi) Did it involve sexual intercourse?

Family interview for genetic studies (FIGS)



Now I am asking you to keep in mind all those in your family as I go through this list of questions

Did anyone:

Feel very low for a couple of weeks or more, or have a diagnosis of depression?

Attempt or complete suicide?

Seem overexcited (or manic) day and night, or have a diagnosis of mania?

Have visions, hear voices, or have beliefs that seem strange or unreal?

Have unusual or bizarre behaviour, or have a diagnosis of schizophrenia?

Was anyone hospitalized for psychiatric problems?

Hamilton depression rating scale (HAM-D)

(To be administered by a health care professional). The HAM-D is designed to rate the severity of depression in patients. Although it contains 21 areas, calculate the patient's score on the first 17 answers. Rate symptoms over the past two weeks

1. DEPRESSED MOOD (Sadness, hopeless, helpless, worthless

0 = Absent

1 = These feeling states indicated only on questioning.

2 = These feeling states spontaneously reported verbally

3 = Communicates feeling states non-verbally – i.e. through facial expression, posture, voice, and tendency to weep.

4 = Patient reports VIRTUALLY ONLY these feeling states in her spontaneous verbal and non-verbal communication.

2. FEELINGS OF GUILT

0 = Absent

1 = Self-reproach, feels she has let people down

2 = Ideas of guilt or rumination over past errors or sinful deeds

3 = Present illness is a punishment; delusions of guilt

4 = Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. SUICIDE

0 = Absent

1 = Feels life is not worth living

2 = Wishes she were dead or any thoughts of possible death to self

3 = Suicidal ideas or gestures

4 = Attempts at suicide (any serious attempt rates 4)

4. INSOMNIA EARLY

0 = No difficulty falling asleep

1 = Complains of occasional difficulty falling asleep – i.e. more than ½ hour

2 = Complains of nightly difficulty falling asleep

5. INSOMNIA MIDDLE

0 = No difficulty

1 = Patient complains of being restless and disturbed during the night

2 = Waking during the night – any getting out of bed rates 2 (except for purposes of voiding)

6. INSOMNIA LATE

0 = No difficulty

1 = Waking in early hours of the morning but goes back to sleep

2 = Unable to fall asleep again if she gets out of bed

7. WORK AND INTERESTS

0 = No difficulty

1 = Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies

2 = Loss of interest in activity, hobbies, or work – either directly reported by patient or indirect in listlessness, indecision and vacillation (feels she has to push self to work or activities)

3 = Decrease in actual time spent in activities or decrease in productivity

4 = Stopped working because of present illness

8. RETARDATION: PSYCHOMOTOR (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

0 = Normal speech and thought

1 = Slight retardation at interview

2 = Obvious retardation at interview

3 = Interview difficult

4 = Complete stupor

9. AGITATION

0 = None

1 = Fidgetiness

2 = Playing with hands, hair, etc.

3 = Moving about, can't sit still

4 = Hand wringing, nail biting, hair-pulling, biting of lips

10. ANXIETY (PSYCHOLOGICAL)

0 = No difficulty

1 = Subjective tension and irritability

2 = Worrying about minor matters

3 = Apprehensive attitude apparent in face or speech

4 = Fears expressed without questioning

11. ANXIETY SOMATIC Physiological concomitants of anxiety, (i.e. effects of autonomic overactivity, "butterflies", indigestion, stomach cramps, belching, diarrhoea, palpitations, hyperventilation, paraesthesia, sweating, flushing, tremor, headache, urinary frequency).

Avoid asking about possible medication side effects (i.e dry mouth, constipation)

0 = Absent

1 = Mild

2 = Moderate

3 = Severe

4 = Incapacitating

12. SOMATIC SYMPTOMS (GASTROINTESTINAL)

0 = None

1 = Loss of appetite but eating without encouragement from others. Food intake about normal

2 = Difficulty eating without urging from others. Marked reduction of appetite and food intake

13. SOMATIC SYMPTOMS GENERAL

0 = Absent

1 = Heaviness in limbs, back or head. Backache, headache, muscle aches. Loss of energy and fatiguability

2 = Any clear cut symptom rates 2

14. GENITAL SYMPTOMS (Symptoms such as: loss of libido, impaired sexual performance; menstrual disturbances)

0 = Absent

1 = Mild

2 = Severe

15. HYPOCHONDRIASIS

0 = Not present

1 = Self-absorption (bodily)

2 = Preoccupation with health

3 = Frequent complaints, requests for help, etc.

4 = Hypochondriacal delusions

16. LOSS OF WEIGHT (N.B. rate N/A [-88] for data entry)

A. When rating by history

0 = No weight loss

1 = Probable weight loss associated with present illness

2 = Definite (according to patient) weight loss

3 = Not assessed

17. INSIGHT (N.B. rate N/A [-88] for participants who do not have a diagnosis of MDD)

0 = Acknowledges being depressed and ill

1 = Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.

2 = Denies being ill at all

18. DIURNAL VARIATION

A. Note whether symptoms are worse in morning or evening. If NO diurnal variation, mark none

0 = No variation

1 = Worse in AM

2 = Worse in P.M.

B. When present, mark severity of the variation. Mark "None" if NO variation.

0 = None

1 = Mild

2 = Severe

19. DEPERSONALIZATION AND DEREALIZATION (Such as: Feelings of unreality, nihilistic ideas)

0 = Absent

1 = Mild

2 = Moderate

3 = Severe

4 = Incapacitating

20. PARANOID SYMPTOMS

0 = None

1 = Suspicious

2 = Ideas of reference

3 = Delusions of reference and persecution

21. OBSESSIONAL AND COMPULSIVE SYMPTOMS

0 = Absent

1 = Mild

2 = Severe

Young mania rating scale (YMRS)

Instructions to researcher: Mainly rated from general observation and interview, rather than from asking direct questions. It may be necessary to ask directly about some subjects, to ensure all areas of the tool are covered. A severity rating is assigned to each of the eleven items, based on the patient's subjective report of her condition over the previous 48 hours and the clinician's behavioural observations during assessment, with the emphasis on the latter.

1. Elevated mood: How might you describe your mood in the last couple of days?

0 = Absent.

1 = Mildly or possibly increased on questioning.

2 = Definite subjective elevation; optimistic, self-confident; cheerful and appropriate to content.

3 = Elevated, inappropriate to content and humorous

4 = Euphoric; inappropriate laughter, singing

2. Increase motor activity/energy: In the last 2 or so days how restless would you say you've been?

0 = Absent.

1 = Subjectively increased.

2 = Animated, gestures increased.

3 = Excessive energy; hyperactive at times; restless (can be calmed).

4 = Motor excitement; continuous hyperactivity.

3. Sexual interest: What about your interest in sex in the last couple of days?

0 = Normal; not increased.

1 = Mildly or possibly increased.

2 = Definite subjective increase on questioning.

3 = Spontaneous sexual content; elaborates on sexual matters; hypersexual by self-report.

4 = Overt sexual acts (towards others).

4. Sleep: How have you been sleeping in the last couple of days?

0 = Reports no decrease in sleep.

1 = Sleeping less than normal amount by up to one hour.

2 = Sleeping less than normal amount by more than one hour.

3 = Reports decreased need for sleep.

4 = Denies need for sleep.

5. Irritability: Have you been more irritable recently?

0 = Absent.

1 = Subjectively increased.

2 = Irritable at times during interview; recent episodes of anger or annoyance on ward.

3 = Frequently irritable during interview; short, curt throughout.

4 = Hostile, uncooperative; interview impossible.

6. Speech (rate and amount): Rate on basis of interview
 - 0 = No increase.
 - 1 = Feels talkative.
 - 2 = Increased rate or amount at times, verbose at times.
 - 3 = Push; consistently increased rate and amount; difficult to interrupt.
 - 4 = Pressured; uninterruptible, continuous speech
7. Language – thought disorder: Rate on basis of interview
 - 0 = Absent.
 - 1 = Circumstantial; mild distractibility; quick thoughts.
 - 2 = Distractible; loses goal of thought; change topics frequently; racing thoughts.
 - 3 = Flight of ideas; tangentiality; difficult to follow; rhyming, echolalia.
 - 4 = Incoherent; communication impossible.
8. Content: Rate on basis of interview
 - 0 = Normal.
 - 1 = Questionable plans, new interests.
 - 2 = Special project(s); hyper-religious.
 - 3 = Grandiose or paranoid ideas; ideas of reference.
 - 4 = Delusions; hallucinations.
9. Disruptive – aggressive behaviour: Rate on basis of interview
 - 0 = Absent, cooperative.
 - 1 = Sarcastic; loud at times, guarded.
 - 2 = Demanding; threats on ward.
 - 3 = Threatens interviewer; shouting; interview difficult.
 - 4 = Assaultive; destructive; interview impossible.
10. Appearance: Rate on basis of interview
 - 0 = Appropriate dress and grooming.
 - 1 = Minimally unkempt.
 - 2 = Poorly groomed; moderately dishevelled; overdressed.
 - 3 = Dishevelled; partly clothed; garish make-up.
 - 4 = Completely unkempt; decorated; bizarre garb.
11. Insight: Do you think you've been unwell in recent days?
 - 0 = Present; admits illness and agrees with need for treatment.
 - 1 = Possibly ill.
 - 2 = Admits behaviour change, but denies illness.
 - 3 = Admits possible change in behaviour, but denies illness.
 - 4 = any behaviour change.
 - 88 = Not unwell

Positive and negative syndrome scale (PANSS)

Instructions to researcher: Tick the box for each symptom which best describes the participant's condition over the last 7 days and not relative to any other time. For more detailed information on each PANSS item, and to make ratings, you should use the PANSS Manual of Definitions

Positive scale

	Absent	Minimal	Mild	Moderate	Mod. severe	Severe	Extreme
1. Delusions	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
2. Conceptual disorganisation	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
3. Hallucinatory behaviour	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
4. Excitement	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
5. Grandiosity	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
6. Suspiciousness /persecution	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
7. Hostility	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7

Negative scale

	Absent	Minimal	Mild	Moderate	Mod. severe	Severe	Extreme
8. Blunted affect	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
9. Emotional withdrawal	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
10. Poor rapport	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
11. Passive/apathetic social withdrawal	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
12. Difficulty in abstract thinking	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
13. Lack of spontaneity and flow of conversation	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
14. Stereotyped thinking	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7

General psychopathology scale

	Absent	Minimal	Mild	Moderate	Mod. severe	Severe	Extreme
15. Somatic concern	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
16. Anxiety	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
17. Guilt feelings	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
18. Tension	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
19. Mannerisms and posturing	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
20. Depression	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
21. Motor retardation	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
22. Uncooperativeness	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
23. Unusual thought content	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
24. Disorientation	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
25. Poor attention	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
26. Lack of judgement and insight	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
27. Disturbance of volition	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
28. Poor impulse control	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
29. Preoccupation	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
30. Active social avoidance	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7

DSM-IV Axis V: Global Assessment of Functioning (GAF) Scale

Consider psychological, social, and occupational functioning on a hypothetical continuum of mental health-illness. Do not include impairment in functioning due to physical (or environmental) limitations.

GAF rating:

current:

highest past year:

CODE (Note: Use intermediate level when appropriate, e.g., 45, 68, 72.)

- 100 Superior functioning in a wide range of activities, life's problems never seem to get out of hand,
I is sought out by others because of his or her many positive qualities. No symptoms
91
- 90 Absent or minimal symptoms (e.g., mild anxiety before an exam), good functioning in all areas,
I interested and involved in a wide range of activities, socially effective, generally satisfied with
81 life, no more than everyday problems or concerns (e.g. an occasional argument with family
members).
- 80 If symptoms are present, they are transient and expectable reactions to psychosocial stressors
I (e.g., difficulty concentrating after family argument), no more than slight impairment in social,
71 occupational, or school functioning (e.g., temporarily falling behind in school work).
- 70 Some mild symptoms (e.g., depressed mood and mild insomnia) OR some difficulty in social,
I occupational, or school functioning (e.g., occasional truancy, or absences from work), but
61 generally functioning pretty well, has some meaningful interpersonal relationships.
- 60 Moderate symptoms (e.g., flat affect and circumstantial speech, occasional panic attacks) OR
I moderate difficulty in social, occupational, or school functioning (e.g., few friends, conflicts
51 with co-workers).
- 50 Serious symptoms (e.g., suicidal ideation, severe obsessional rituals, frequent shoplifting) OR
I any serious impairment in social, occupational, or school functioning (e.g., no friends, unable to
41 keep a job).
- 40 Some impairment in reality testing or communication (e.g., speech is at times illogical, obscure,
I or irrelevant) OR major impairment in several areas, such as work or school, family relations,
I judgment, thinking, or mood (e.g., depressed man avoids friends, neglects family, and is unable
31 to work; child frequently beats up younger children, is defiant at home, and is failing at school).
- 30 Behaviour is considerably influenced by delusions or hallucinations OR serious impairment in
I communication or judgment (e.g., sometimes incoherent, acts grossly inappropriately, suicidal
I preoccupation) OR inability to function in almost all areas (e.g., stays in bed all day; no job,
21 home, or friends)
- 20 Some danger of hurting self or others (e.g., suicide attempts without clear expectation of death,
I frequently violent, manic excitement) OR occasionally fails to maintain minimal personal
11 hygiene (e.g., smears feces) OR gross impairment in communication (e.g., largely incoherent or
mute)
- 10 Persistent danger of severely hurting self or others (e.g., recurrent violence) OR persistent
I inability to maintain minimal personal hygiene OR serious suicide act with clear expectation of
1 death

0 Inadequate information

Clinical global impression (CGI)
Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- 1 Not assessed
- 2 Normal, not at all ill
- 3 Borderline mentally ill
- 4 Mildly ill
- 5 Moderately ill
- 6 Markedly ill
- 7 Severely ill
- 8 Among the most extremely ill patients.

Beck depression inventory (BDI)

Choose one statement from among the group of four statements in each question that best describes how you have been feeling during the past few days. Circle the number beside your choice.

1. 0. I do not feel sad.
 1. I feel sad.
 2. I am sad all the time and I can't snap out of it.
 3. I am so sad or unhappy that I can't stand it.
2. 0. I am not particularly discouraged about the future.
 1. I feel discouraged about the future.
 2. I feel I have nothing to look forward to.
 3. I feel that the future is hopeless and that things cannot improve.
3. 0. I do not feel like a failure.
 1. I feel I have failed more than the average person.
 2. As I look back on my life, all I can see is a lot of failure.
 3. I feel I am a complete failure as a person.
4. 0. I get as much satisfaction out of things as I used to.
 1. I don't enjoy things the way I used to.
 2. I don't get any real satisfaction out of anything anymore.
 3. I am dissatisfied or bored with everything.
5. 0. I don't feel particularly guilty.
 1. I feel guilty a good part of the time.
 2. I feel quite guilty most of the time.
 3. I feel guilty all of the time.
6. 0. I don't feel I am being punished.
 1. I feel I may be punished.
 2. I expect to be punished.
 3. I feel I am being punished.
7. 0. I don't feel disappointed in myself.
 1. I am disappointed in myself.
 2. I am disgusted with myself.
8. 0. I don't feel I am any worse than anybody else.
 1. I am critical of myself for my weaknesses or mistakes.
 2. I blame myself all the time for my faults.
 3. I blame myself for everything bad that happens.
9. 0. I don't have any thoughts of killing myself.

1. I have thoughts of killing myself, but I would not carry them out.
 2. I would like to kill myself.
 3. I would kill myself if I had the chance.
-
10. 0. I don't cry any more than usual.
 1. I cry more than I used to.
 2. I cry all the time now.
 3. I used to be able to cry, but now I can't cry even though I want to.
-
11. 0. I am no more irritated by things than I ever am.
 1. I am slightly more irritated now than usual.
 2. I am quite annoyed or irritated a good deal of the time.
 3. I feel irritated all the time now.
-
12. 0. I have not lost interest in other people.
 1. I am less interested in other people than I used to be.
 2. I have lost most of my interest in other people.
 3. I have lost all of my interest in other people.
-
13. 0. I make decisions about as well as I ever could.
 1. I put off making decisions more than I used to.
 2. I have greater difficulty in making decisions than before.
 3. I can't make decisions at all anymore
-
14. 0. I don't feel that I look any worse than I used to.
 1. I am worried that I am looking old or unattractive.
 2. I feel that there are permanent changes in my appearance that make me look unattractive.
 3. I believe that I look ugly.
-
15. 0. I can work about as well as before.
 1. It takes an extra effort to get started at doing something.
 2. I have to push myself very hard to do anything.
 3. I can't do any work at all.
-
16. 0. I can sleep as well as usual.
 1. I don't sleep as well as I used to.
 2. I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
 3. I wake up several hours earlier than I used to and cannot get back to sleep.
-
17. 0. I don't get more tired than usual.
 1. I get tired more easily than I used to.
 2. I get tired from doing almost anything.
 3. I am too tired to do anything.
-
18. 0. My appetite is no worse than usual.

1. My appetite is not as good as it used to be.
 2. My appetite is much worse now.
 3. I have no appetite at all anymore.
-
19. 0. I haven't lost much weight, if any, lately.
 1. I have lost more than five pounds.
 2. I have lost more than ten pounds.
 3. I have lost more than fifteen pounds.
-
20. 0. I am no more worried about my health than usual.
 1. I am worried about physical problems such as aches and pains, or upset stomach, or constipation.
 2. I am very worried about physical problems, and it's hard to think of much else.
 3. I am so worried about my physical problems that I cannot think about anything else.
-
21. 0. I have not noticed any recent change in my interest in sex.
 1. I am less interested in sex than I used to be.
 2. I am much less interested in sex now.
 3. I have lost interest in sex completely.

Perceived stress scale (PSS)

The questions in this scale ask you about your feelings and thoughts during the last month. In each case, please indicate with a tick how often you felt or thought a certain way.

Please write here the time of day at which this questionnaire was completed

In the last month, how often have you been upset because of something that happened unexpectedly?

- | | | | |
|--------------|--------------------------|--------------|--------------------------|
| Never | <input type="checkbox"/> | Fairly often | <input type="checkbox"/> |
| Almost never | <input type="checkbox"/> | Very often | <input type="checkbox"/> |
| Sometimes | <input type="checkbox"/> | | |

In the last month, how often have you felt that you were unable to control the important things in your life?

- | | | | |
|--------------|--------------------------|--------------|--------------------------|
| Never | <input type="checkbox"/> | Fairly often | <input type="checkbox"/> |
| Almost never | <input type="checkbox"/> | Very often | <input type="checkbox"/> |
| Sometimes | <input type="checkbox"/> | | |

In the last month, how often have you felt nervous and "stressed"?

- | | | | |
|--------------|--------------------------|--------------|--------------------------|
| Never | <input type="checkbox"/> | Fairly often | <input type="checkbox"/> |
| Almost never | <input type="checkbox"/> | Very often | <input type="checkbox"/> |
| Sometimes | <input type="checkbox"/> | | |

In the last month, how often have you felt confident about your ability to handle your personal problems?

- | | | | |
|--------------|--------------------------|--------------|--------------------------|
| Never | <input type="checkbox"/> | Fairly often | <input type="checkbox"/> |
| Almost never | <input type="checkbox"/> | Very often | <input type="checkbox"/> |
| Sometimes | <input type="checkbox"/> | | |

In the last month, how often have you felt that things were going your way?

- | | | | |
|--------------|--------------------------|--------------|--------------------------|
| Never | <input type="checkbox"/> | Fairly often | <input type="checkbox"/> |
| Almost never | <input type="checkbox"/> | Very often | <input type="checkbox"/> |
| Sometimes | <input type="checkbox"/> | | |

In the last month, how often have you found that you could not cope with all the things that you had to do?

- | | | | |
|--------------|--------------------------|--------------|--------------------------|
| Never | <input type="checkbox"/> | Fairly often | <input type="checkbox"/> |
| Almost never | <input type="checkbox"/> | Very often | <input type="checkbox"/> |
| Sometimes | <input type="checkbox"/> | | |

In the last month, how often have you been able to control irritations in your life?

- | | | | |
|--------------|--------------------------|--------------|--------------------------|
| Never | <input type="checkbox"/> | Fairly often | <input type="checkbox"/> |
| Almost never | <input type="checkbox"/> | Very often | <input type="checkbox"/> |
| Sometimes | <input type="checkbox"/> | | |

In the last month, how often have you felt that you were on top of things?

- | | | | |
|--------------|--------------------------|--------------|--------------------------|
| Never | <input type="checkbox"/> | Fairly often | <input type="checkbox"/> |
| Almost never | <input type="checkbox"/> | Very often | <input type="checkbox"/> |
| Sometimes | <input type="checkbox"/> | | |

In the last month, how often have you been angered because of things that were outside of your control?

- | | | | |
|--------------|--------------------------|--------------|--------------------------|
| Never | <input type="checkbox"/> | Fairly often | <input type="checkbox"/> |
| Almost never | <input type="checkbox"/> | Very often | <input type="checkbox"/> |
| Sometimes | <input type="checkbox"/> | | |

In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

- | | | | |
|--------------|--------------------------|--------------|--------------------------|
| Never | <input type="checkbox"/> | Fairly often | <input type="checkbox"/> |
| Almost never | <input type="checkbox"/> | Very often | <input type="checkbox"/> |
| Sometimes | <input type="checkbox"/> | | |

Self- evaluation questionnaire (STAI; state)

A number of statements which people have used to describe themselves are given below. Read each statement and then tick in the appropriate box on the right to indicate how you feel right now, that is, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately so	Very much so
I feel calm	1	2	3	4
I feel secure	1	2	3	4
I feel tense	1	2	3	4
I feel strained	1	2	3	4
I feel at ease	1	2	3	4
I feel upset	1	2	3	4
I am presently worrying over possible misfortunes	1	2	3	4
I feel satisfied	1	2	3	4
I feel frightened	1	2	3	4
I feel comfortable	1	2	3	4
I feel self-confident	1	2	3	4
I feel nervous	1	2	3	4
I am jittery	1	2	3	4
I feel indecisive	1	2	3	4
I am relaxed	1	2	3	4
I feel content	1	2	3	4
I am worried	1	2	3	4
I feel confused	1	2	3	4
I feel steady	1	2	3	4
I feel pleasant	1	2	3	4

Self- evaluation questionnaire (STAI; trait)

A number of statements which people have used to describe themselves are given below. Read each statement and then tick in the appropriate box on the right to indicate how you generally feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

	Almost never	Sometimes	Often	Almost always
I feel pleasant	1	2	3	4
I feel nervous and restless	1	2	3	4
I feel satisfied with myself	1	2	3	4
I wish I could be as happy as others seem to be	1	2	3	4
I feel like a failure	1	2	3	4
I feel rested	1	2	3	4
I am "calm, cool, and collected"	1	2	3	4
I feel that difficulties are piling up so that I cannot overcome them	1	2	3	4
I worry too much over something that really does not matter	1	2	3	4
I am happy	1	2	3	4
I have disturbing thoughts	1	2	3	4
I lack self-confidence	1	2	3	4
I feel secure	1	2	3	4
I make decisions easily	1	2	3	4
I feel inadequate	1	2	3	4
I am content	1	2	3	4
Some unimportant thought runs through my mind and bothers me	1	2	3	4
I take disappointments so keenly that I cannot put them out of my mind	1	2	3	4
I am a steady person	1	2	3	4
I get in a state of tension or turmoil as I think over my recent concerns and interests	1	2	3	4

Athens insomnia scale (AIS)

This scale is intended to record your own assessment of any sleep difficulty you might have experienced. Please check (by circling the appropriate number) the items below to indicate your estimate of any difficulty, provided that it occurred at least three times per week during the last 2 weeks.

Sleep induction (time it takes you to fall asleep after turning-off the lights)

- 0 No problem
- 1 Slightly delayed
- 2 Markedly delayed
- 3 Very delayed or did not sleep at all

Awakenings during the night

- 0 No problem
- 1 Minor problem
- 2 Considerable problem
- 3 Serious problem or did not sleep at all

Final awakening earlier than desired

- 0 Not earlier
- 1 A little earlier
- 2 Markedly earlier
- 3 Much earlier or did not sleep at all

Total sleep duration

- 0 Sufficient
- 1 Slightly insufficient
- 2 Markedly insufficient
- 3 Very insufficient or did not sleep at all

Overall quality of sleep (no matter how long you slept)

- 0 Satisfactory
- 1 Slightly unsatisfactory
- 2 Markedly unsatisfactory
- 3 Very unsatisfactory or did not sleep at all

Sense of well-being during the day

- 0 Normal
- 1 Slightly decreased
- 2 Markedly decreased
- 3 Very decreased

Functioning (physical and mental) during the day

- 0 Normal
- 1 Slightly decreased
- 2 Markedly decreased
- 3 Very decreased

Sleepiness during the day

- 0 None
- 1 Mild
- 2 Considerable
- 3 Intense

Appendix B

Prescribed medication at the time of the MRI scan in the “at risk group”.

Table 1 CGA

Medication	Dose mg/day	Exposure in days	CPZ equivalent mg/day
<i>Antipsychotics + additional</i> (N=14)			
Olanzapine	3	682	60
Olanzapine	5	47	100
Olanzapine, Lithium	5, 1000	515, 18	100, NA
Olanzapine	10	8	200
Olanzapine, Citalopram	10, 30	59	200, NA
Olanzapine, Valproate semisodium	10, 500	784	200, NA
Olanzapine	15	85	300
Quetiapine	13	24	17
Quetiapine	400	398	533
Quetiapine	400	520	533
Quetiapine	600	26	800
Risperidone, Promethazine	12, 25	68	600, NA
Olanzapine	unknown	233	NA
Haloperidol	unknown	unknown	NA
<i>Antidepressants</i> (N=3)			
Citalopram	unknown	unknown	NA
Fluoxetine	60	202	NA
Sertraline	unknown	unknown	NA
<i>Benzodiazepines + additional</i> (N=1)			
Clonazepam, Zopiclone	unknown, 8	41	NA

Table 1 shows the prescribed medication for the “at risk” group at the time of the MRI scan. The dose is displayed in milligram per day. The length of exposure is displayed in days. Chlorpromazine (CPZ) equivalents have been calculated based on (Woods, 2003). Each row equals one participant (N=1).

Prescribed medication at the time of the MRI scan in the NPE and PE groups.

Table 2 SGA

<i>Medication</i>	<i>Dose mg/day</i>	<i>Exposure in days</i>	<i>CPZ equivalent mg/day</i>
NPE group (N=7)			
<i>Antipsychotics + additional</i>			
Olanzapine	5	47	100
Olanzapine, Valproate semisodium	10, 500	784	200, NA
Quetiapine	400	398	533
Quetiapine	400	520	533
Haloperidol	unknown	unknown	NA
<i>Antidepressants</i>			
Fluoxetine	60	202	NA
Sertraline	unknown	unknown	NA
PE group (N=11)			
<i>Antipsychotics + additional</i>			
Olanzapine	3	682	60
Olanzapine, Lithium	5, 1000	515, 18	100, NA
Olanzapine	10	8	200
Olanzapine, Citalopram	10, 30	59	200, NA
Olanzapine	15	85	300
Quetiapine	13	24	17
Quetiapine	600	26	800
Risperidone, Promethazine	12, 25	68	600, NA
Olanzapine	unknown	233	NA
<i>Antidepressants</i>			
Citalopram	unknown	unknown	NA
<i>Benzodiazepines + additional</i>			
Clonazepam, Zopiclone	unknown, 8	41	NA

Table 2 shows the prescribed medication for the “at risk” group at the time of the MRI scan. The dose is displayed in milligram per day. The length of exposure is displayed in days. Chlorpromazine (CPZ) equivalents have been calculated based on (Woods, 2003). Each row equals one participant (N=1).

Appendix C

First-degree relatives with a psychiatric illness in the “at risk” group.

Table 3 (CGA)

Relative	Psychiatric illness
<i>At risk group</i> (N=15)	
Mother / Sister	PP / PD & anxiety
Mother	BD
Brother	BD
Father	Psychotic episode
Brother / Father, Mother & Brother	BD / MDD
Father & Mother	MDD
Father	MDD
Mother / Sister	MDD and PTSD / Anxiety & anorexia
Mother	MDD
Mother	MDD
Mother	MDD
Mother	MDD
Mother	MDD
Sister	MDD
Brother / Mother	MDD / Anorexia & agoraphobia
<i>Healthy controls</i> (N=3)	
Sister	MDD
Father	MDD
Mother	MDD

Table 3 PP=postpartum psychosis. PD=postpartum depression. BD=bipolar disorder. MDD=major depressive disorder. PTSD=post-traumatic stress disorder. Each row equals one participant (N=1).

First-degree relatives with a psychiatric illness in the NPE and PE groups.

Table 4 First-degree relatives with a psychiatric illness (SGA)

Relative	Psychiatric illness
<i>NPE group</i> (N=10)	
Mother	BD
Father	Psychotic episode
Brother / Father, Mother & Brother	BD / MDD
Father & Mother	MDD
Mother / Sister	MDD and PTSD / Anxiety & anorexia
Mother	MDD
Mother	MDD
Mother	MDD
Sister	MDD
Brother / Mother	MDD / Anorexia & agoraphobia
<i>PE group</i> (N=4)	
Brother	BD
Mother	MDD
Mother	MDD
Father	MDD
<i>Healthy controls</i> (N=3)	
Sister	MDD
Father	MDD
Mother	MDD

Table 4 PP=postpartum psychosis. PD=postpartum depression. BD=bipolar disorder. MDD=major depressive disorder. PTSD=post-traumatic stress disorder. Each row equals one participant (N=1).

Appendix D

**Institute of
Psychiatry**

at The Maudsley

King's College Hospital 
NHS Foundation Trust

KING'S
College
LONDON

University of London

INFORMATION SHEET (I)

STUDY TITLE

**Risk factors of perinatal mental disorders:
Stress, Electrophysiological, and Neuroimaging markers.
(Research ethics Committee number: 10/H0807/14)**

A study conducted at the Institute of Psychiatry and funded by the National Alliance for Research on Schizophrenia and Depression (NARSAD).

Principal Contact for general queries:

Astrid Pauls Astrid.Pauls@kcl.ac.uk

Chief Investigator: Dr. Paola Dazzan, Institute of Psychiatry, London SE5 8AF

We would like to invite you to take part in a research study at the Institute of Psychiatry. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. The information is separated into two parts. Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. If you do decide to participate, you will be given a copy of this document to take home with you.

PART I

Purpose of the research

It is commonly believed that pregnancy is a time of good mental health. However, severe mental health problems occur around pregnancy (e.g. depression (feeling sad, withdrawn, not motivated) or postpartum psychosis (hearing voices, having bizarre and unshakable beliefs)). These problems can have huge consequences for mother and child. Yet, little research has been done in this area. In this study we want to examine whether there are changes, in response to stress, hormones, or in brain functioning, that can help us identify which women are most likely to develop these problems. Furthermore, we want to investigate how these problems affect the development of the baby. To achieve this, we aim to evaluate women who are at high risk or suffer from mental health problems around pregnancy and women who are at low risk of mental health problems around pregnancy, and their babies. We will look at the way mothers respond to stress, or whether there are changes in parts of the brain, or in the way these areas function, that makes them more likely to become unwell with the hormonal changes that happen around pregnancy. We will also look at whether these problems are associated with changes in the way the baby responds to stress and in the way he/she develops.

Why have I been invited?

We invited you to participate in our study as a healthy control because you are pregnant, and routine screening at your initial meeting with your midwife has not identified you as someone at risk for mental health problems. In total, we will include 150 pregnant women of which 100 will be at high and 50 at low risk for mental health problems. We will also include you baby after he/she is born.

Do I have to take part?

It is entirely up to you to decide whether or not to take part. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. You are

free to withdraw at any time, without giving a reason; this would not affect the standard of care you receive.

What will happen to me and my baby if I take part?

There will be up to 6 study visits, lasting 2-4 hours, over up to 18 months. The study itself will go on for four years in total.

Visit 1

Occurs when you are about 25 weeks pregnant. You will be seen by a clinical researcher who will ask you some background questions such as age, number of children, employment and ethnic origin. You will also complete clinical questionnaires and be asked about any problems you might experience concerning your mental health. You will have a blood test (20mls blood - about 1 tablespoon) to look at hormone levels and to assess your DNA. The researcher may also obtain background information from your medical notes. We are looking at cortisol (“stress hormone”) levels in saliva samples and you will be asked to provide saliva samples, which you can collect yourself on one of the following days after the visit. We will show you how to do this during your first visit.

Visit 2

Occurs shortly after the first visit. We will ask you again to complete some clinical questionnaires. In order to have a look at potential volume or function changes in brain areas, we will invite you to have a Magnetic Resonance Imaging (MRI) scan in our Centre for Neuroimaging Science shortly after your delivery. Therefore, during the current visit we will give you the opportunity to become familiar with our MRI scanner. You will be given the opportunity to lie in a mock-up scanner before lying in the real scanner. We will take a picture of your brain structure in the real scanner. We will also do a neurocognitive assessment, during which you will do some short tasks measuring domains such as attention or memory. Depending on how you feel, we will record the electrical activity of your brain with electroencephalography (EEG). For this, you would have to sit still for 5-10 minutes and consequently

perform some simple cognitive tasks on a computer screen lasting approximately 20 minutes.

After this visit you will receive some short questionnaires by post and we will ask you to complete those and send them back to us, together with another set of saliva samples collected in the same way as during your first study visit.

Visit 3

This visit will take place shortly after your baby is born. We will ask you to fill in some questionnaires and answer questions concerning your mental health. Again, you will have a blood test to look at hormone levels (20mls blood - about 1 tablespoon) and you will be asked to provide specimens of your saliva.

During this scanning session (which will take about 90 minutes), we will collect pictures (scans) of your head while you are performing some simple cognitive tasks or while doing nothing (at rest). We use a very modern method of scanning known as Magnetic Resonance Imaging (MRI). This technique is commonly used to diagnose a number of diseases, but in this case it has been adapted to take images of which parts of your brain are active when you perform a task. When a part of your brain is more active, more blood flows to that region. We will make a map of which parts of your brain has more blood flow than others. In order for us to take pictures of your brain, you will have to lie as still as possible in the MRI scanner. The scanner consists of a powerful magnet, but you will not feel any force or special sensation inside a magnetic field because your body is insensitive to it. Because of the magnetic field, you must not have a scan if you have received metal injuries to your eyes, had metallic objects (including clips) inserted into your body during an operation, or if you have received a gun shot injury or have a heart pace maker. The radiographer will go through a list of possible risks with you before you go into the scanner. Please note that MRI scans do not involve any form of ionising radiation (X-rays), but the scanner itself can be a bit claustrophobic; therefore please inform us if you have a fear of enclosed spaces. All the time you are in the scanner there will be a microphone switched on so you can talk to us. We will talk to you regularly to

explain what will happen next. Some people find the machine noisy, but the headphones we provide allow adequate acoustic protection for most people.

Important:

During the scan your baby can stay at the ward under the care of midwives. If you have already left the ward, a developmental psychologist who has been working in perinatal psychiatry for over 30 years will be available to assist with the care of your baby.

Again, depending on how you feel, we will record the electrical activity of your brain with electroencephalography (EEG). For this, you would have to sit still for 5-10 minutes and consequently perform some simple cognitive tasks on a computer screen lasting approximately 20 minutes.

Following the delivery of your baby, the midwives will take a small section of the umbilical cord or some blood from the umbilical cord after it has been removed from your baby. We will use this to look at the baby's DNA for genetic studies. A study visit is not required at this stage; the sample will be collected by the researcher at a later point.

Visit 4

At 6 days postpartum we would like to assess the behaviour and development of your baby using the Neonatal Behavioural Assessment Scale (NBAS). This assessment looks at the full range of neonatal behaviour, including competencies and strengths, in autonomic stability, motor organization; state organization, and self-quieting capacities. This assessment will last about 20-30 minutes. The researcher will collect a specimen of your baby's saliva shortly before and after the assessment, to look at levels of the stress hormone, cortisol, cotinine (a marker of exposure to tobacco) and DNA, and ask you to complete some brief questionnaires.

Visit 5

This visit will take place 8 weeks after delivery. Similar to visit 1, you will be seen by a clinical researcher who will ask you some background questions such as employment. You will also complete clinical questionnaires and be asked about any problems you might experience concerning your mental health. The researcher may also obtain background information from your medical notes. Again, you will be asked to provide saliva samples, which you can collect yourself on one of the following days after the visit.

We would also like to look at the interactions between you and your baby. In order to do this we will make a 3-5 minute video recording, for which you will be asked to play and talk to your baby as you normally would. We will also obtain saliva samples from your baby, to look at “stress hormone” levels, cotinine and DNA. The clinical researcher will meet with you & your baby when you attend for the baby’s routine vaccinations, & show you how to obtain the sample.

Visit 6

This visit will take part 1 year after delivery. Similar to visit 3, we will ask you to fill in questionnaires and ask questions concerning your mental health; you will have a blood test and you will be asked to provide specimens of your saliva. In order to have a look at potential volume or function changes in brain areas we might invite you again to be scanned in our Centre for Neuroimaging Science record or also record the electrical activity of your brain with electroencephalography (EEG).

We will also assess the behaviour and development of your baby again, and look at the interactions between you and your baby by making a new 3-5 minute video recording as in visit 5. We will also ask questions about baby’s feeding and medication, and maternal medications and collect saliva samples of your baby.

The study assessments are over and above those involved in standard care; normal treatment will not be withheld during the study and will continue as needed after this.

All video recordings are treated as confidential, will not be used for commercial purposes and will be destroyed when the study is completed.

Expenses and payments.

You will be reimbursed for travel expenses you incur in attending for study visits and receive £40 for the scanning visits.

What will I have to do?

If you wish to take part in the study, you will be asked to sign the consent form at the end of this document; you will be given a copy to keep. You should be prepared to undertake the 6 study visits, as detailed above. Please also consider that in agreeing to participate, you are also providing consent on behalf of the baby you are expecting.

What are the possible disadvantages and risks of taking part?

You may find the study visits/procedures inconvenient, particularly after your baby is born, as this is often a busy period for new mothers. It is also possible that you may experience some minor discomfort and/or bruising from the blood test. Although it is not painful, your baby may experience some distress on collection of saliva samples.

During the study, it is possible that other conditions are discovered of which you were unaware, which may have implications for your future health, or otherwise impact on your interests. If anything is identified, your GP or hospital consultant will be informed, with your agreement.

What are the possible benefits of taking part?

There are no direct benefits to you of taking part in the study; however the knowledge gained from this study may be of help to other people in the future.

What do I do if I want to withdraw from the study?

You are free to withdraw from the study at any time you like. You will not be required to give us any reasons for withdrawal from the study but please inform us as soon as possible if you wish to do so. This would not affect the standard of care you receive.

Will my participation be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. More information on confidentiality is given in Part II of this information sheet.

If you have any questions about matters related to the study please contact Astrid Pauls (Astrid.Pauls@kcl.ac.uk) or Dr. Paola Dazzan (Paola.Dazzan@kcl.ac.uk or on 0207 848 0070).

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

PART II

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (tel. 0207 848 0070). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure; details can be obtained from the hospital.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence, then you may have grounds for a legal action for compensation against King's College Hospital Foundation NHS Trust or the study sponsor, King's College London, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

What will happen if I don't want to carry on with the study?

If you withdraw from the study we will destroy all identifiable information about you. We will retain and continue to use any data collected before such withdrawal of consent unless you request that you do not want us to use any data collected from you.

Will my taking part in this study be kept confidential?

Yes, your confidentiality will be safeguarded during and after the study, which is conducted in accordance with the Data Protection Act 1998. An identification code will be allocated to you and later to your baby. The information we collect will be recorded and put into electronic databases using this code rather than your name. Paper and electronic records are stored securely at the Institute of Psychiatry; the custodian of all study materials is Dr Paola Dazzan (Chief Investigator).

The researchers will have access to your clinical notes and those of your baby. By signing the consent, you will be giving consent for the researchers to examine your notes and those of your baby.

Study data will be analysed and results will be submitted for publication; your identity will not be revealed. Study data will be retained and may be used in future studies, if this happens, further Research Ethics Committee approval will be sought. Authorized persons such as researchers, sponsors, regulatory authorities and Research and Development audit will have access to view identifiable data, for monitoring of the quality of the research. Study data will be retained for 10 years after completion of the study; and will be disposed of securely. You have the right to check the accuracy of data held about you and correct any errors according to local law and procedures.

What will happen to any samples I give?

All samples from you and your baby will be processed and then stored prior to analysis using the identification code described. The researchers and laboratory scientists will have access to the samples; the researcher will be able to link your other study data to data from the analysis of your sample by the identification code. All samples will be disposed in accordance with the Human Tissue Authority's Code of Practice once the study is completed.

What will happen to the results of the research study?

The data and results from this study may be published in medical journals or used in scientific reports and may be communicated to the regulatory authorities. You will not be identified by name. Once the study has been completed, a report of the findings will be prepared for participants; you can request a copy using the contact details below.

Who is organising and funding the research?

The Chief Investigator, Dr. Paola Dazzan is organizing the research, which is sponsored by the Institute of Psychiatry, King's College London, and funded by the National Alliance for Research on Schizophrenia and Depression (NARSAD), the EU, and the Foundation for Prevention of Sudden Infant Death. The researchers

involved in conducting this study do not receive any financial incentives for including you in this study and do not benefit financially from this study.

Who has reviewed the study?

This research has been looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed by Joint SLAM/IOP Research ethics Committee Ref number: 10/H0807/14.

If you have any questions about matters related to the study please contact Astrid Pauls (Astrid.Pauls@kcl.ac.uk) or Dr. Paola Dazzan (Paola.Dazzan@kcl.ac.uk or on 0207 848 0070).

You will receive a copy of the information leaflet and signed consent form to keep.

Thank you for reading this information sheet.

INFORMATION SHEET (II)

STUDY TITLE

**Risk factors of perinatal mental disorders:
Stress, Electrophysiological, and Neuroimaging markers.
(Research ethics Committee number: 10/H0807/14)**

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Astrid Pauls Astrid.Pauls@kcl.ac.uk

Chief Investigator: Dr. Paola Dazzan, Institute of Psychiatry, London SE5 8AF

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PART I

Purpose of the research

It is commonly believed that pregnancy is a time of good mental health. However, severe mental health problems occur around pregnancy (e.g. depression (feeling sad, withdrawn, not motivated) or postpartum psychosis (hearing voices, having bizarre and unshakable beliefs)). These problems can have huge consequences for mother and child. Yet, little research has been done in this area. In this study we want to examine whether there are changes, in response to stress, hormones, or in brain functioning, that can help us identify which women are most likely to develop these problems. Furthermore, we want to investigate how these problems affect the development of the baby. To achieve this, we aim to evaluate women who are at high risk or suffer from mental health problems around pregnancy and women who are at low risk of mental health problems around pregnancy, and their babies. We will look at the way mothers respond to stress, or whether there are changes in parts of the brain, or in the way these areas function, that makes them more likely to become unwell with the hormonal changes that happen around pregnancy. We will also look at whether these problems are associated with changes in the way the baby responds to stress and in the way he/she develops.

Why have I been invited?

We invited you to participate in our study because you are pregnant and your midwife or another healthcare professional have identified you as someone who may be at risk of developing, or actually suffering from, mental health problems. In total, we will include 150 pregnant women of which 100 will be at high and 50 at low risk for mental health problems. We would also like to include your baby after he/she is born.

Do I have to take part?

It is entirely up to you to decide whether or not to take part. We will describe the study and go through this information sheet, which we will then give to you. We will

then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason; this would not affect the standard of care you receive.

What will happen to me and my baby if I take part?

There will be up to 6 study visits, lasting 2-4 hours, over up to 18 months. The study itself will go on for four years in total.

Visit 1

Occurs when you are about 25 weeks pregnant. You will be seen by a clinical researcher who will ask you some background questions such as age, number of children, employment and ethnic origin. You will also complete clinical questionnaires and be asked about any problems you might experience concerning your mental health. You will have a blood test (20mls blood - about 1 tablespoon) to look at hormone levels and to assess your DNA. The researcher may also obtain background information from your medical notes. We are looking at cortisol (“stress hormone”) levels in saliva samples and you will be asked to provide saliva samples, which you can collect yourself on one of the following days after the visit. We will show you how to do this during your first visit.

Visit 2

Occurs shortly after the first visit. We will ask you again to complete some clinical questionnaires. In order to have a look at potential volume or function changes in brain areas, we will invite you to have a Magnetic Resonance Imaging (MRI) scan in our Centre for Neuroimaging Science shortly after your delivery. Therefore, during the current visit we will give you the opportunity to become familiar with our MRI scanner. You will be given the opportunity to lie in a mock-up scanner before lying in the real scanner. We will take a picture of your brain structure in the real scanner. We will also do a neurocognitive assessment, during which you will do some short tasks measuring domains such as attention or memory. Depending on how you feel, we will record the electrical activity of your brain with electroencephalography

(EEG). For this, you would have to sit still for 5-10 minutes and consequently perform some simple cognitive tasks on a computer screen lasting approximately 20 minutes.

After this visit you will receive some short questionnaires by post and we will ask you to complete those and send them back to us, together with another set of saliva samples collected in the same way as during your first study visit.

Visit 3

This visit will take place shortly after your baby is born. We will ask you to fill in some questionnaires and answer questions concerning your mental health. Again, you will have a blood test to look at hormone levels (20mls blood - about 1 tablespoon) and you will be asked to provide specimens of your saliva.

During this scanning session (which will take about 90 minutes), we will collect pictures (scans) of your head while you are performing some simple cognitive tasks or while doing nothing (at rest). We use a very modern method of scanning known as Magnetic Resonance Imaging (MRI). This technique is commonly used to diagnose a number of diseases, but in this case it has been adapted to take images of which parts of your brain are active when you perform a task. When a part of your brain is more active, more blood flows to that region. We will make a map of which parts of your brain has more blood flow than others. In order for us to take pictures of your brain, you will have to lie as still as possible in the MRI scanner. The scanner consists of a powerful magnet, but you will not feel any force or special sensation inside a magnetic field because your body is insensitive to it. Because of the magnetic field, you must not have a scan if you have received metal injuries to your eyes, had metallic objects (including clips) inserted into your body during an operation, or if you have received a gun shot injury or have a heart pace maker. The radiographer will go through a list of possible risks with you before you go into the scanner. Please note that MRI scans do not involve any form of ionising radiation (X-rays), but the scanner itself can be a bit claustrophobic; therefore please inform us if you have a fear of enclosed spaces. All the time you are in the scanner there will be a

microphone switched on so you can talk to us. We will talk to you regularly to explain what will happen next. Some people find the machine noisy, but the headphones we provide allow adequate acoustic protection for most people.

Important:

During the scan your baby can stay at the ward under the care of midwives. If you have already left the ward, a developmental psychologist who has been working in perinatal psychiatry for over 30 years will be available to assist with the care of your baby.

Again, depending on how you feel, we will record the electrical activity of your brain with electroencephalography (EEG). For this, you would have to sit still for 5-10 minutes and consequently perform some simple cognitive tasks on a computer screen lasting approximately 20 minutes.

Following the delivery of your baby, the midwives will take a small section of the umbilical cord or some blood from the umbilical cord after it has been removed from your baby. We will use this to look at the baby's DNA for genetic studies. A study visit is not required at this stage; the sample will be collected by the researcher at a later point.

Visit 4

At 6 days postpartum we would like to assess the behaviour and development of your baby using the Neonatal Behavioural Assessment Scale (NBAS). This assessment looks at the full range of neonatal behaviour, including competencies and strengths, in autonomic stability, motor organization; state organization, and self-quieting capacities. This assessment will last about 20-30 minutes. The researcher will collect a specimen of your baby's saliva shortly before and after the assessment, to look at levels of the stress hormone, cortisol, cotinine (a marker of exposure to tobacco) and DNA, and ask you to complete some brief questionnaires.

Visit 5

This visit will take place 8 weeks after delivery. Similar to visit 1, you will be seen by a clinical researcher who will ask you some background questions such as employment. You will also complete clinical questionnaires and be asked about any problems you might experience concerning your mental health. The researcher may also obtain background information from your medical notes. Again, you will be asked to provide saliva samples, which you can collect yourself on one of the following days after the visit.

We would also like to look at the interactions between you and your baby. In order to do this we will make a 3-5 minute video recording, for which you will be asked to play and talk to your baby as you normally would. We will also obtain saliva samples from your baby, to look at “stress hormone” levels, cotinine and DNA. The clinical researcher will meet with you & your baby when you attend for the baby’s routine vaccinations, & show you how to obtain the sample.

Visit 6

This visit will take part 1 year after delivery. Similar to visit 3, we will ask you to fill in questionnaires and ask questions concerning your mental health; you will have a blood test and you will be asked to provide specimens of your saliva. In order to have a look at potential volume or function changes in brain areas we might invite you again to be scanned in our Centre for Neuroimaging Science record or also record the electrical activity of your brain with electroencephalography (EEG).

We will also assess the behaviour and development of your baby again, and look at the interactions between you and your baby by making a new 3-5 minute video recording as in visit 5. We will also ask questions about baby’s feeding and medication, and maternal medications and collect saliva samples of your baby.

The study assessments are over and above those involved in standard care; normal treatment will not be withheld during the study and will continue as needed after this.

All video recordings are treated as confidential, will not be used for commercial purposes and will be destroyed when the study is completed.

Expenses and payments.

You will be reimbursed for travel expenses you incur in attending for study visits and receive £40 for the scanning visits.

What will I have to do?

If you wish to take part in the study, you will be asked to sign the consent form at the end of this document; you will be given a copy to keep. You should be prepared to undertake the 6 study visits, as detailed above. Please also consider that in agreeing to participate, you are also providing consent on behalf of the baby you are expecting.

What are the possible disadvantages and risks of taking part?

You may find the study visits/procedures inconvenient, particularly after your baby is born, as this is often a busy period for new mothers. It is also possible that you may experience some minor discomfort and/or bruising from the blood test. Although it is not painful, your baby may experience some distress on collection of saliva samples.

During the study, it is possible that other conditions are discovered of which you were unaware, which may have implications for your future health, or otherwise impact on your interests. If anything is identified, your GP or hospital consultant will be informed, with your agreement.

What are the possible benefits of taking part?

There are no direct benefits to you of taking part in the study; however the knowledge gained from this study may be of help to other people in the future.

What do I do if I want to withdraw from the study?

You are free to withdraw from the study at any time you like. You will not be required to give us any reasons for withdrawal from the study but please inform us as soon as possible if you wish to do so. This would not affect the standard of care you receive.

Will my participation be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. More information on confidentiality is given in Part II of this information sheet.

If you have any questions about matters related to the study please contact Astrid Pauls (Astrid.Pauls@kcl.ac.uk) or Dr. Paola Dazzan (Paola.Dazzan@kcl.ac.uk or on 0207 848 0070).

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

PART II

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (tel. 0207 848 0070). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure; details can be obtained from the hospital.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence, then you may have grounds for a legal action for compensation against King's College Hospital Foundation NHS Trust or the study sponsor, King's College London, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

What will happen if I don't want to carry on with the study?

If you withdraw from the study we will destroy all identifiable information about you. We will retain and continue to use any data collected before such withdrawal of consent unless you request that you do not want us to use any data collected from you.

Will my taking part in this study be kept confidential?

Yes, your confidentiality will be safeguarded during and after the study, which is conducted in accordance with the Data Protection Act 1998. An identification code will be allocated to you and later to your baby. The information we collect will be recorded and put into electronic databases using this code rather than your name. Paper and electronic records are stored securely at the Institute of Psychiatry; the custodian of all study materials is Dr Paola Dazzan (Chief Investigator).

The researchers will have access to your clinical notes and those of your baby. By signing the consent, you will be giving consent for the researchers to examine your notes and those of your baby.

Study data will be analysed and results will be submitted for publication; your identity will not be revealed. Study data will be retained and may be used in future studies, if this happens, further Research Ethics Committee approval will be sought. Authorized persons such as researchers, sponsors, regulatory authorities and Research and Development audit will have access to view identifiable data, for monitoring of the quality of the research. Study data will be retained for 10 years after completion of the study; and will be disposed of securely. You have the right to check the accuracy of data held about you and correct any errors according to local law and procedures.

What will happen to any samples I give?

All samples from you and your baby will be processed and then stored prior to analysis using the identification code described. The researchers and laboratory scientists will have access to the samples; the researcher will be able to link your other study data to data from the analysis of your sample by the identification code. All samples will be disposed in accordance with the Human Tissue Authority's Code of Practice once the study is completed.

What will happen to the results of the research study?

The data and results from this study may be published in medical journals or used in scientific reports and may be communicated to the regulatory authorities. You will not be identified by name. Once the study has been completed, a report of the findings will be prepared for participants; you can request a copy using the contact details below.

Who is organising and funding the research?

The Chief Investigator, Dr. Paola Dazzan is organizing the research, which is sponsored by the Institute of Psychiatry, King's College London, and funded by the National Alliance for Research on Schizophrenia and Depression (NARSAD), the EU, and the Foundation for Prevention of Sudden Infant Death. The researchers

involved in conducting this study do not receive any financial incentives for including you in this study and do not benefit financially from this study.

Who has reviewed the study?

This research has been looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed by Joint SLAM/IOP Research ethics Committee Ref number: 10/H0807/14.

If you have any questions about matters related to the study please contact Astrid Pauls (Astrid.Pauls@kcl.ac.uk) or Dr. Paola Dazzan (Paola.Dazzan@kcl.ac.uk or on 0207 848 0070).

You will receive a copy of the information leaflet and signed consent form to keep.

Thank you for reading this information sheet.

Study Title: Risk factors of perinatal mental disorders: Stress, Electrophysiological, and Neuroimaging markers. (Research ethics Committee number: 10/H0807/14)

Principal Contact for general queries:

Astrid Pauls, Institute of Psychiatry, London SE5 8AF, Email: Astrid.Pauls@kcl.ac.uk

Chief Investigator: Dr. Paola Dazzan, Institute of Psychiatry, London SE5 8AF

Telephone: 0207 848 0070

AGREEMENT TO PARTICIPATE

Participant ID:	
Your Consent	Please initial each box
1. I confirm that I have read and understood the information sheet dated 02.06.10 (Version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered.	
2. I understand that my participation is voluntary and that I am free to withdraw anytime without giving any reason and without my medical care or legal rights being affected.	
3. I give permission to members of the research team (Institute of Psychiatry) to access the sections of my clinical medical notes that are relevant to the study.	
4. I understand that members of research team at the Institute of Psychiatry will have access to the data from this study and agree not to restrict the use of any data or results, which arise from this study.	
5. I agree that my GP or hospital consultant will be informed if, during the study, other conditions are discovered of which I was unaware.	
6. I agree to take part in the above study, and that my baby will be included after birth.	

Printed name of participant

Printed name of person explaining consent

I have explained the study to the participant and answered all questions with regard to the study honestly and fully.

Signature of participant

Date

Signature of person explaining consent

Date

Who is invited to take part in our research?

We are contacting pregnant women who plan to have their baby at King's College Hospital, London, to invite them to participate in our study.

If you are approached by one of our researchers, it is entirely up to you whether or not you take part.



When are research participants seen?

- During pregnancy
- Shortly after delivery
- Eight weeks after delivery
- One year after delivery

Visits can take place in participants' homes, at King's College Hospital, or at our nearby research centre.



Outcomes of our research programme

Results from our research programme will be used to improve clinical practice with pregnant and postnatal women and their babies and to inform future studies of stress in pregnancy.

If you would like more information about the PRAM Programme:

email: pram@kcl.ac.uk

or call: 020 7848 0353

Psychiatry Research and Motherhood,
PO71, Section of Perinatal Psychiatry,
Kings College London,
De Crespigny Park,
London
SE5 8AF

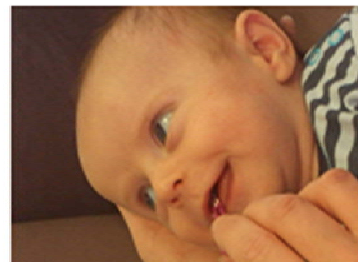


The PRAM Programme

Although pregnancy is often thought to be a time of good mental health, it can be a time when women feel stressed.

We are studying the effects of stress and mental health problems during pregnancy by comparing women with and without these difficulties.

The aim is to understand how stress and mental health problems interact with biological systems in the body during pregnancy and the effects they may have on the baby after birth.



What do we ask research participants to do?

- **During pregnancy**

We visit participants and ask about their pregnancy and their psychological health.



We also collect samples of saliva and blood to measure hormone levels and the other biological systems we are studying.

- **Shortly after delivery**

Six days after delivery we visit the mother and baby and demonstrate the amazing abilities of the newborn.

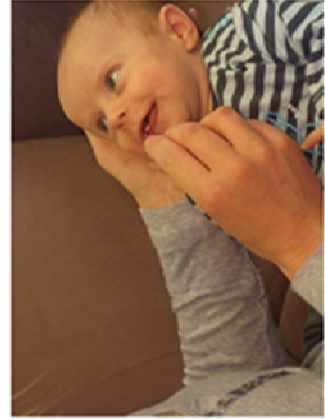
Some women may be invited to have a brain scan where we collect pictures of the brain during the performance of some simple tasks.



- **Eight weeks after delivery**

We visit participants again and ask about their psychological health since delivery.

We also collect saliva samples from the baby to measure hormones before and after the routine immunisations.



- **One year after delivery**

We repeat the eight week assessments and collect saliva samples from the baby before and after the routine 12 month immunisations.

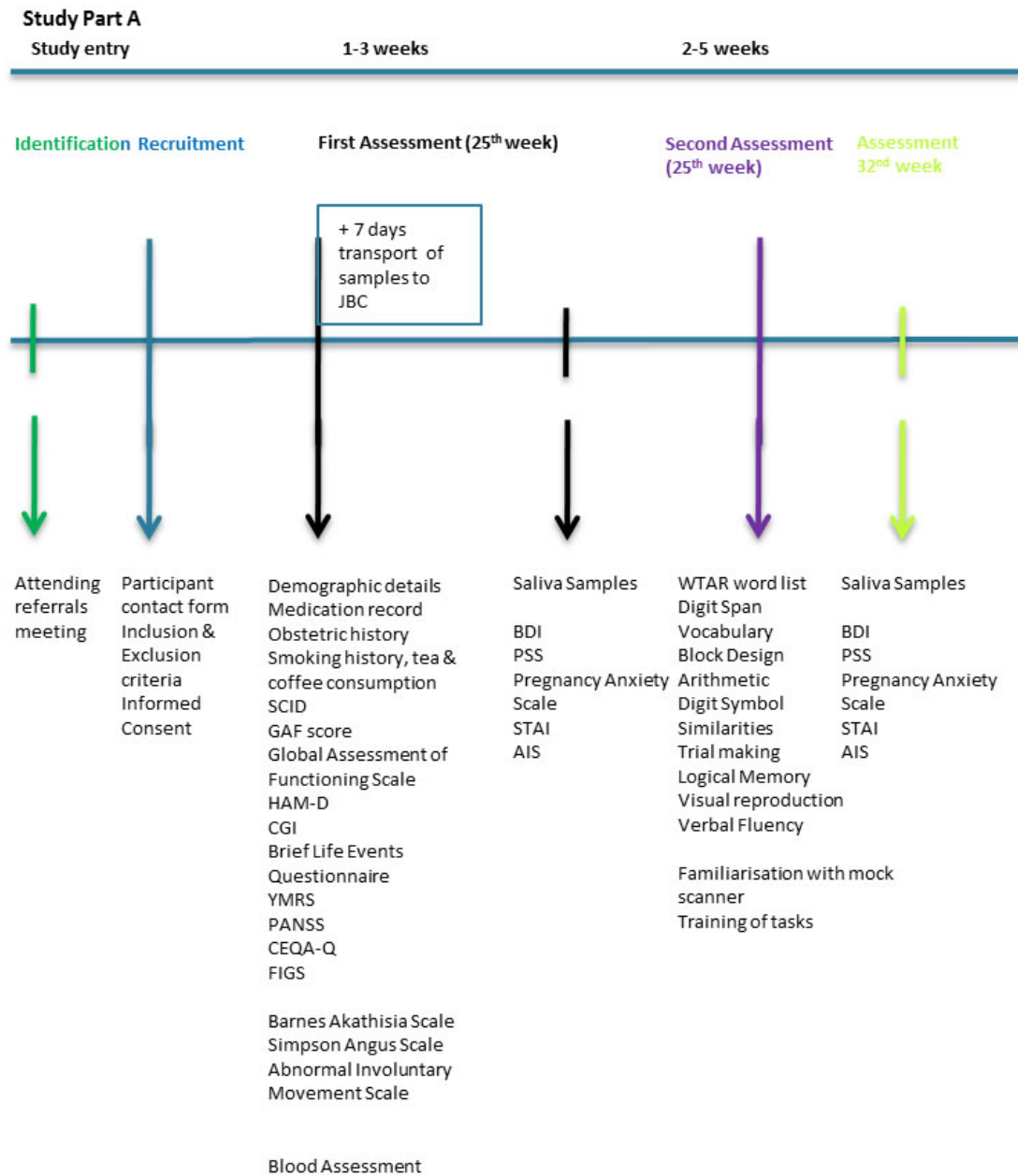


We also carry out a developmental assessment of the baby.

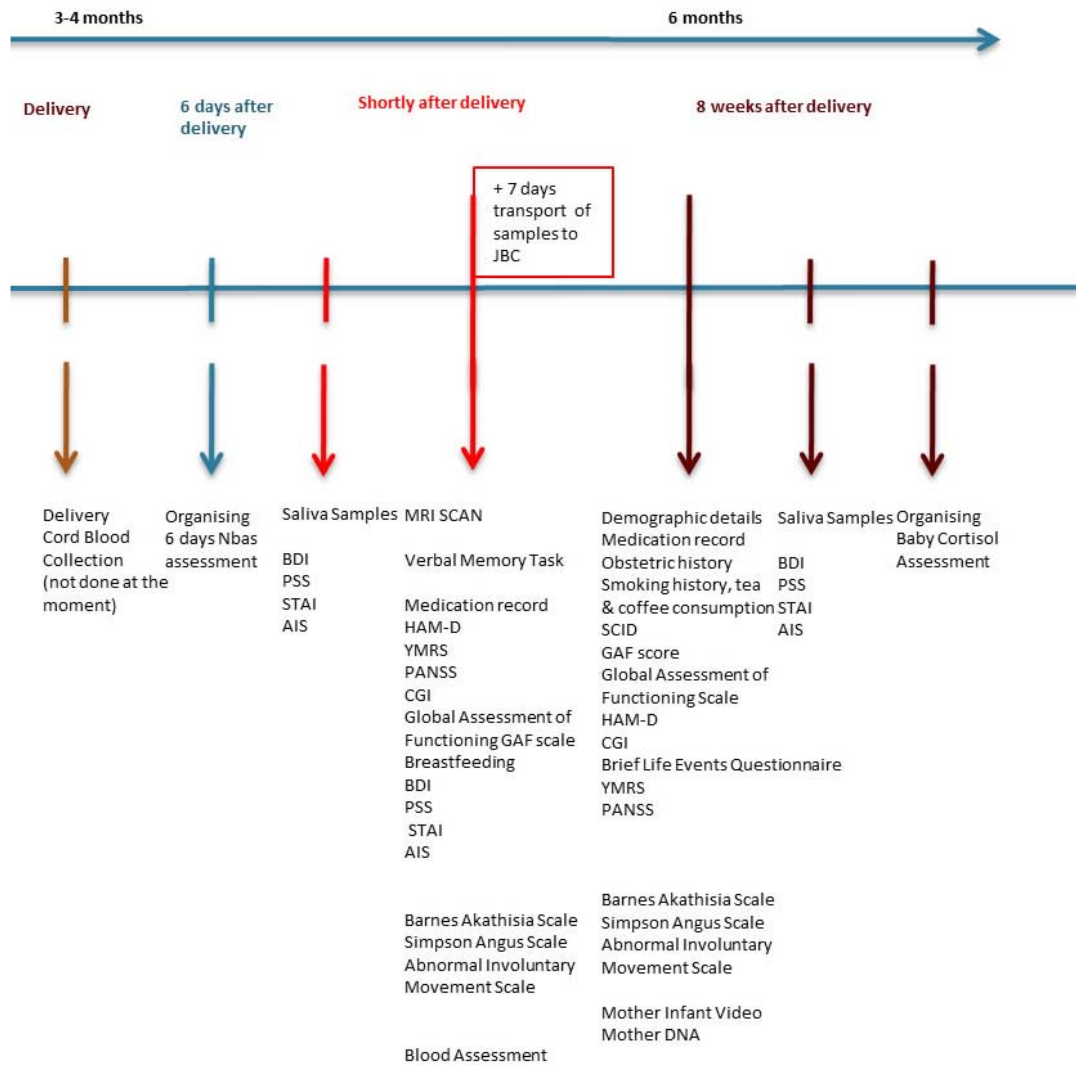


Appendix E

Original study design (page 1 of 2)



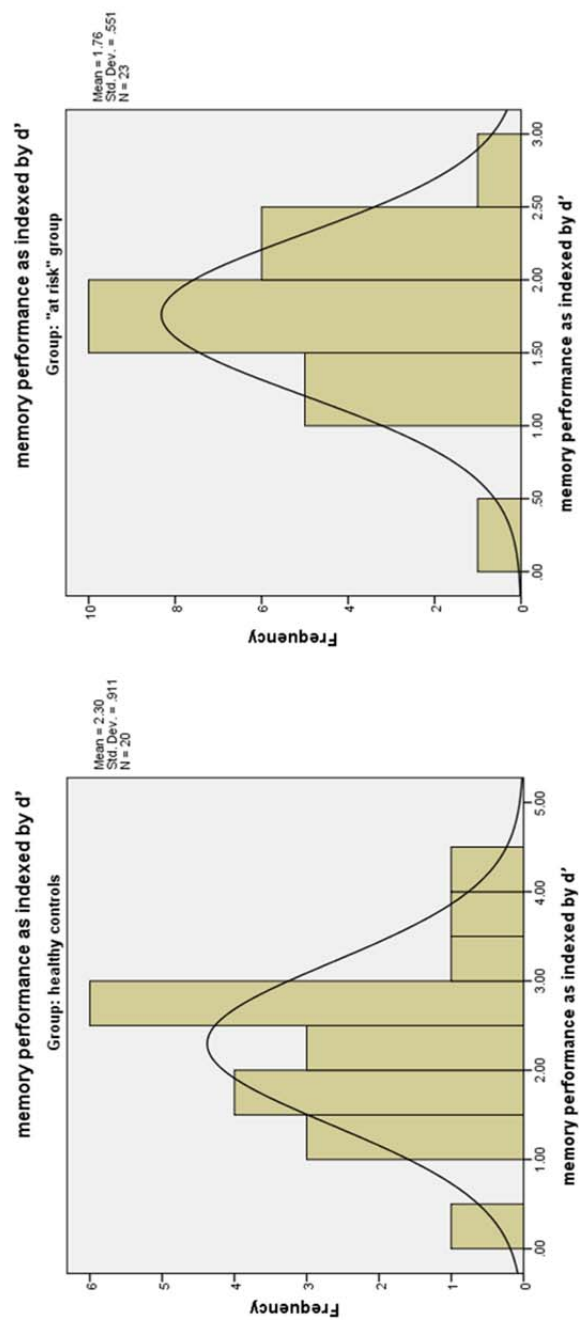
Original study design (page 2 of 2)



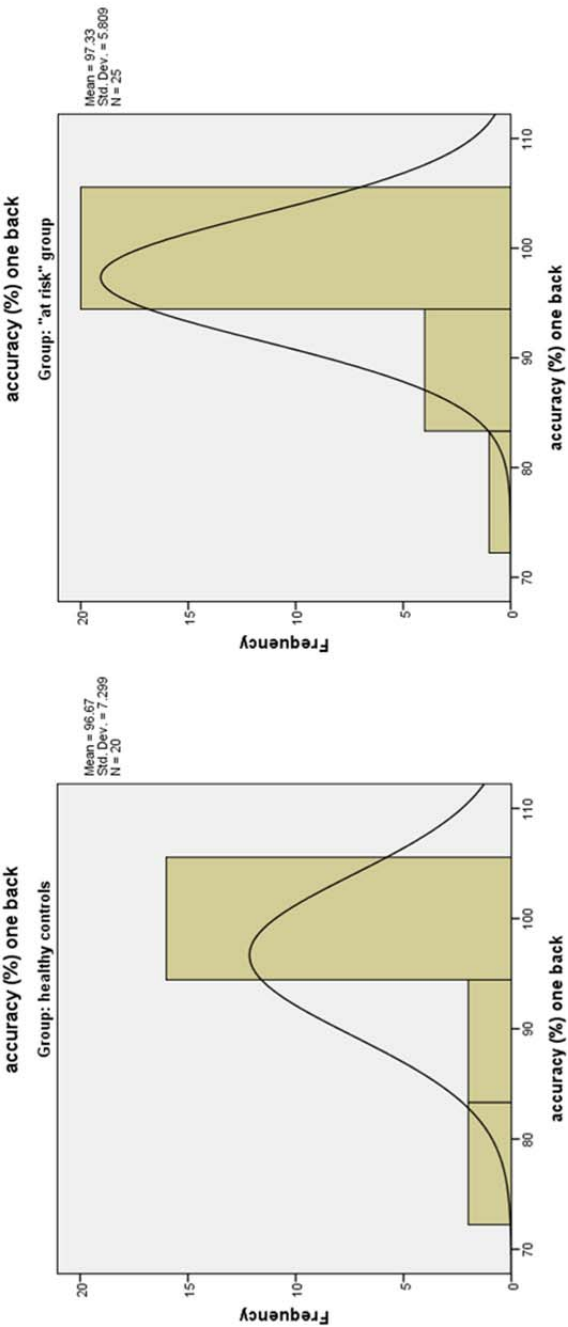
Appendix F

Frequency distributions of the performance and activation data of verbal memory, working memory, and facial emotion processing

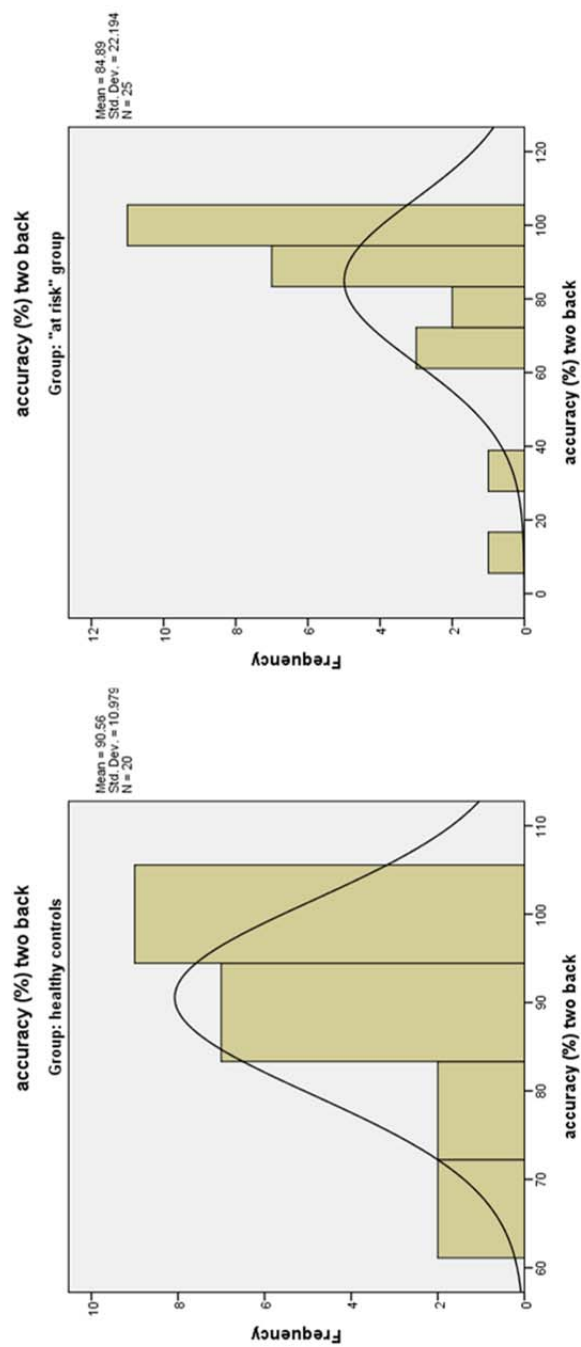
Verbal memory



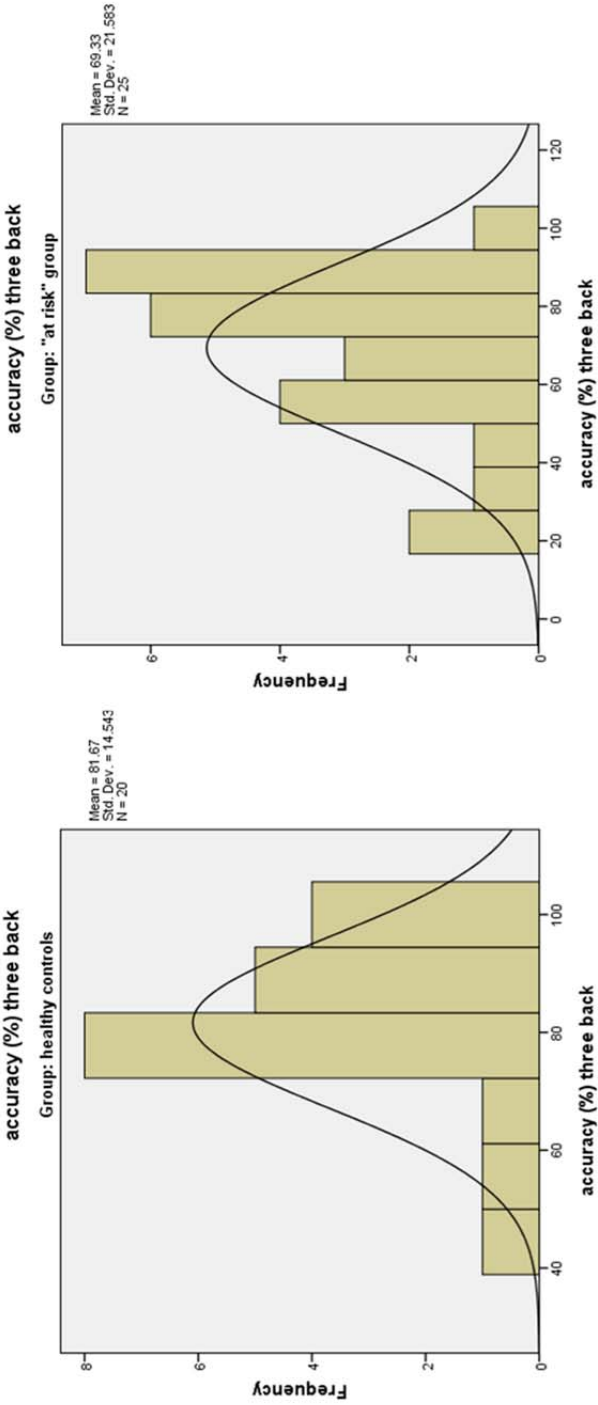
Working memory (I)



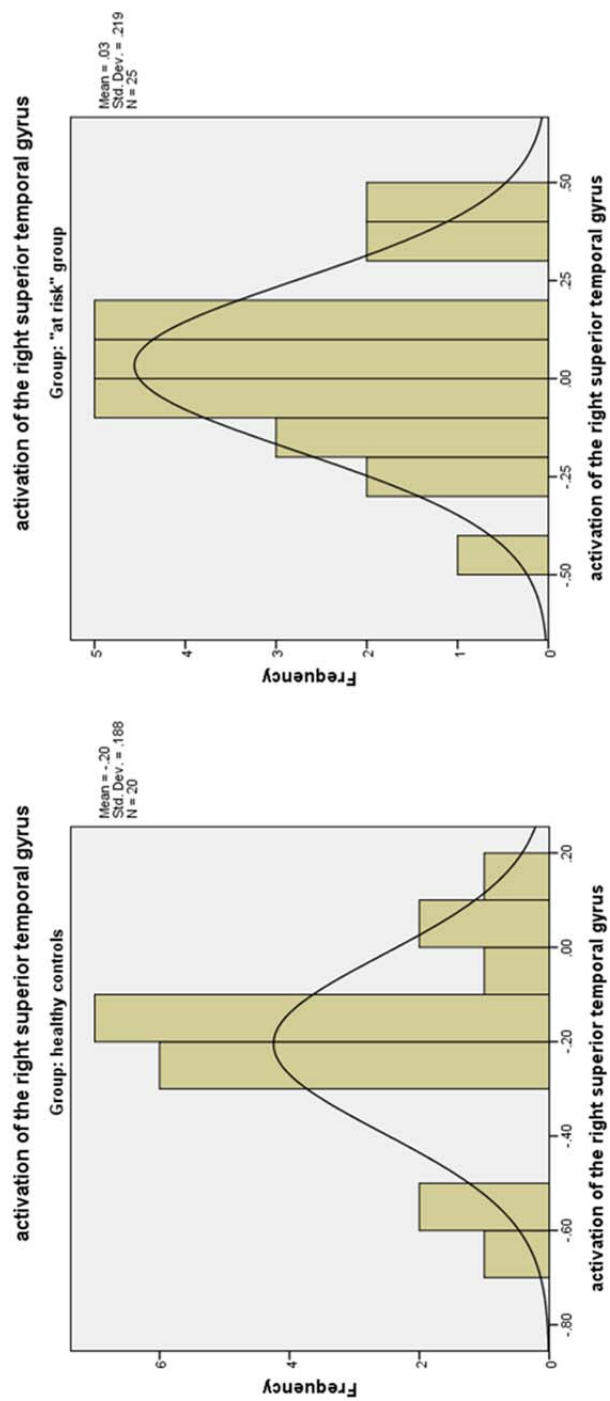
Working memory (II)



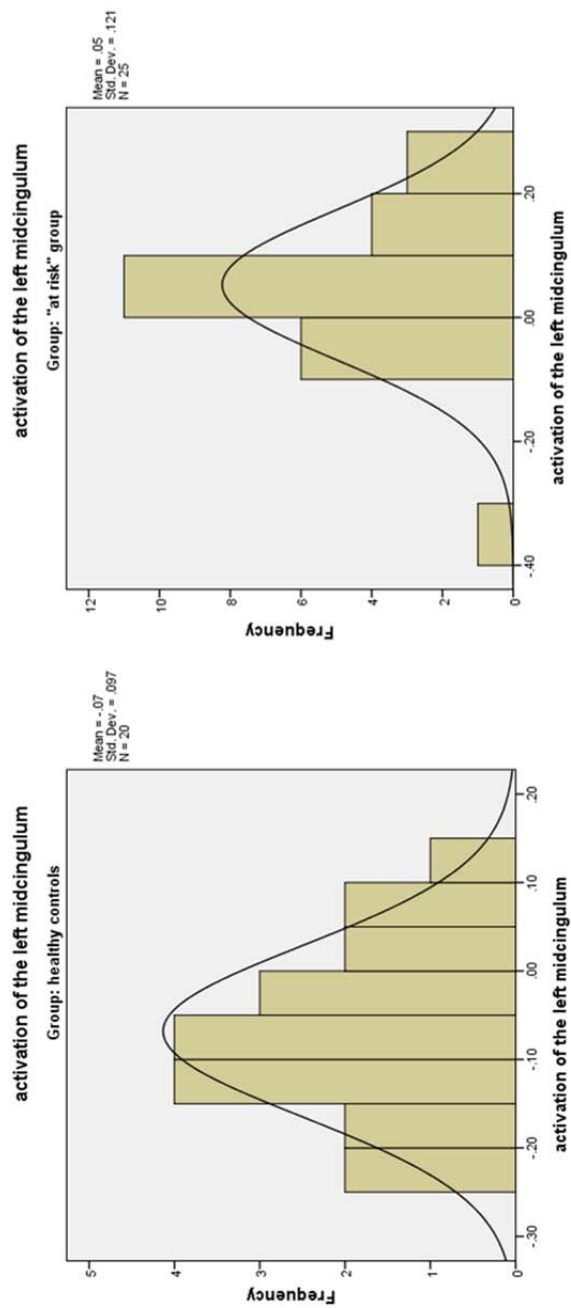
Working memory (III)



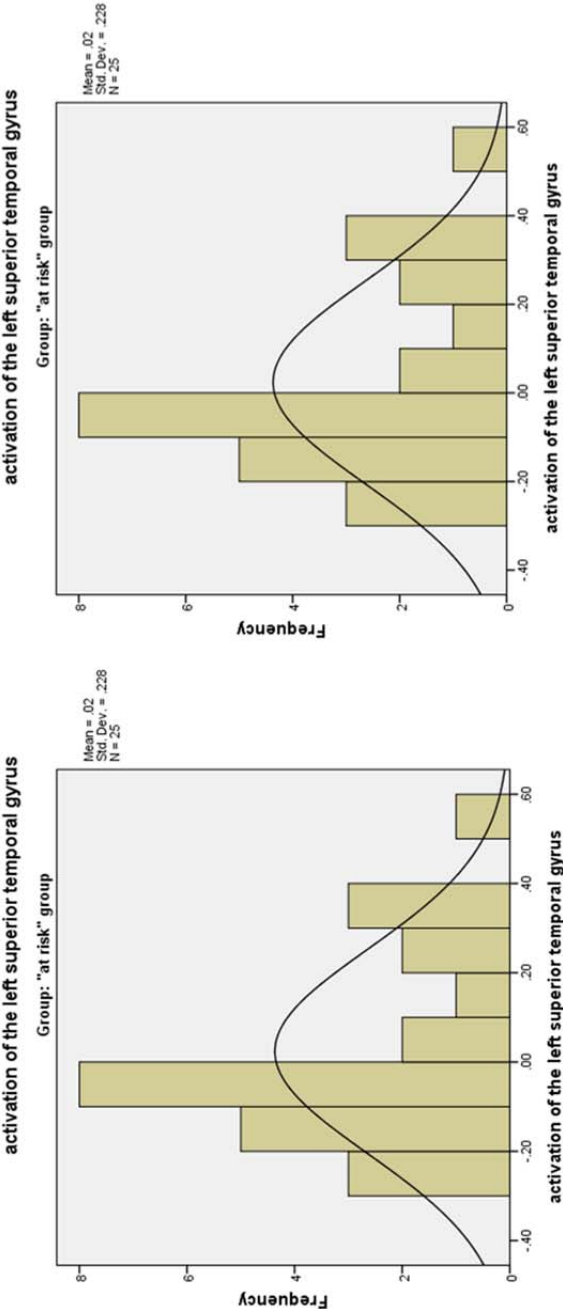
Working memory (IV)



Working memory (V)



Working memory (VI)



Facial emotion processing

